Esophageal Cancer

Diagnosis and Treatment

Francisco Schlottmann
Daniela Molena
Marco G. Patti
Editors

Springer

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Editors
Francisco Schlottmann
Hospital Alemán of Buenos Aires
University of Buenos Aires
Buenos Aires
Argentina

Daniela Molena
Memorial Sloan Kettering
Cancer Center
New York, NY
USA

Marco G. Patti
University of North Carolina
at Chapel Hill
Chapel Hill, NC
USA

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To our mothers, with gratitude for their unconditional support of our quest for a better education

Maria Cristina Pozzi
Luigina Bondesan
Ada Travali Patti

Preface

Esophageal cancer is the eighth most common cancer worldwide, with an estimated 456,000 new cases and 400,000 deaths in 2012. About 87% of all esophageal cancers globally are squamous cell carcinomas, with the highest incidence rates in populations within South-Eastern and Central Asia, Eastern Africa, and South America. Only 11% of all esophageal cancers are esophageal adenocarcinomas, with an elevated burden seen in Northern and Western Europe, Oceania, and Northern America. Over the past 40 years, however, the incidence of esophageal adenocarcinoma has increased more than sixfold in Western countries. This increased incidence has been mostly attributed to the rising prevalence of obesity and gastroesophageal reflux disease.

This evidence- and experience-based book represents the collaboration of leading centers in the world in the treatment of esophageal cancer. This book is a state-of-the-art description of the multidisciplinary management of esophageal cancer, from diagnosis to treatment. All topics are treated by world-renowned experts, stressing the importance of a multidisciplinary approach in the care of these patients. For this reason, the expected audience will be physicians in the fields of surgery, gastroenterology, and medical oncology.

Buenos Aires, Argentina — Francisco Schlottmann
New York, NY, USA — Daniela Molena
Chapel Hill, NC, USA — Marco G. Patti

Contents

About the Editors

Francisco Schlottmann, MD, MPH received his medical degree with honors at the University of Buenos Aires in Argentina. He then completed his general surgery residency at the Hospital Alemán of Buenos Aires. After his surgical training, Dr. Schlottmann completed the Soudavar fellowship at Memorial Sloan Kettering Cancer Center, focusing his research on esophageal cancer. He then did a 2-year gastrointestinal surgery fellowship at the University of North Carolina. Dr. Schlottmann obtained his Master of Public Health at the University of North Carolina Gillings School of Global Public Health. He currently serves as an Associate Professor of Surgery at the Hospital Alemán of Buenos Aires with an active clinical and research interest in esophageal and gastric diseases.

Daniela Molena, MD received her medical degree from the University of Padova in Italy. She completed her general surgery residency at the University of Padova and at the University of Rochester Medical Center. She then completed the following fellowships: Gastrointestinal Surgery (University of California San Francisco); Minimally Invasive Surgery (University of Padova); Cardiothoracic Surgery (New York Presbyterian/Weill Cornell Medical Center); and Cardiothoracic Surgery (Memorial Sloan Kettering Cancer Center). After completing her training, Dr. Molena was appointed as Assistant Professor at John Hopkins Medical Center. Currently, she serves as Director of Memorial Sloan Kettering's Esophageal Program, where she strives to provide excellent and individualized care to patients and to integrate new technology and novel approaches to the Thoracic Oncology Service.

Marco G. Patti, MD is a Professor of Medicine and Surgery at the University of North Carolina. He graduated from the University of Catania, Italy, and completed a research fellowship and residency in general surgery at the University of California San Francisco (UCSF). He then did a fellowship in esophageal cancer at the Queen Mary Hospital in Hong Kong. He served as faculty at UCSF for 14 years and at the University of Chicago for 8 years. In 2016, he moved to the University of North Carolina in Chapel Hill as Professor of Medicine and Surgery and Co-director of the Center of Esophageal Diseases and Swallowing. His research in esophageal diseases is reflected in numerous publications and books.

Introduction

Esophageal cancer is the eighth most commonly diagnosed malignancy and is associated with the sixth highest cancer mortality worldwide. More than 400,000 deaths were recorded in 2012, primarily focused in East Asia. A disease of such magnitude deserves the attention of specialists focused on its diagnosis and management.

In this volume, Drs. Schlottmann, Molena, and Patti have created an impressive overview as a resource for clinicians, patients and families, industry, and others interested in esophageal cancer. The book is unique in the breadth of its scope, ranging from anatomy, pathogenesis, and epidemiology to multidisciplinary care and future prospects for screening and treatment. The list of authors reads as a "who's who" among esophageal cancer specialists. Its international flavor renders it a notable contribution to the field that will be used by specialists in the East and West alike.

The epidemiology of esophageal cancer is fascinating. As highlighted in this book, one can appreciate that wide range of cultural, economic, and genetic influences on its incidence and histology. The change from predominance of squamous cancer to adenocarcinoma in the West during the latter third of the twentieth century and the incursions of adenocarcinoma into East Asian society during the first part of the twenty-first century exemplify how gradual alterations in diet, exercise, and other habits can influence the occurrence of life-threatening diseases.

Too often non-surgical specialists regard the surgical management of esophageal cancer as a "black box," whereas the details of systemic therapy and radiation therapy are both easy to describe and quantify in delivery and outcomes. This volume unpacks the mysteries of surgical philosophies and approaches so that all specialists may understand the nuances of an important treatment modality that exposes esophageal cancer patients to a considerable risk of morbidity and mortality while simultaneously offering appropriately selected patients the best chance of cure.

Of particular interest to many specialists will be the chapter on volume-outcome relationships. In many areas of the world, regionalization of esophageal cancer care has occurred spontaneously (China, Japan) or has been mandated by government (England, Canada, the Netherlands) in order to improve overall standards of care and outcomes. Spontaneous regionalization effects are becoming evident in the USA as well. The overall benefits of such regionalization have yet to be conclusively demonstrated, and in some

countries, regionalization has limited access to care because of the increased travel distances that are required to reach a specialized center.

Many readers will be interested in the chapters on quality of life and palliative care. For a disease that has a typical 5-year survival of about 15%, quality of life is of paramount importance to many patients. This aspect is also reflected in the increasing international focus on patient reported outcomes after treatment, which historically have been underreported and undervalued.

To discuss all of the highlights in this book is beyond the capacity of a short Introduction. The editors and authors have produced an informative, readable, and authoritative resource that will facilitate esophageal cancer care worldwide for years to come. This volume will become a standard reference, and I personally look forward to seeing new editions in the future as progress in the field is made.

Chicago, USA Mark K. Ferguson

Esophageal Anatomy

1

Mariano A. Menezes, Rafael O. Sato,
Francisco Schlottmann,
and Fernando A. M. Herbella

Introduction

The esophagus has a peculiar anatomy. It is the only digestive organ that does not digest or absorb nutrients and lacks a serosa layer. From a surgical anatomy point of view, the esophagus has an exuberant lymphatic drainage able to spread metastasis quickly and far but is short of vascularization without a single artery bearing its name. The esophagus crosses three cavities (neck, thorax and abdomen) and it is surrounded by vital organs in the mediastinum [1]. All these characteristics make the resection of the esophagus and the subsequent alimentary tract reconstruction a challenging and morbid procedure.

Anatomists frequently portrait the esophagus in didactic books in a stylized fashion commonly not useful for surgeons. In addition, minimally invasive surgery also brought a restricted but magnified view of the esophagus, and available imaging technology forces the understanding of sectional and regional anatomy. Thus, a strong knowledge of the anatomy of the esophagus is essential to all esophageal surgeons interested in performing an esophagectomy.

Esophageal Anatomy

The esophagus is a hollow organ with a four-layer structure: mucosa, submucosa, muscularis propria, and adventitia [2]. The mucosa is made of squamous epithelium overlying a lamina propria and a muscularis mucosa. The submucosa is made of elastic and fibrous tissue and is the strongest layer of the esophageal wall. The esophageal muscle is composed of an inner circular and outer longitudinal layer. The upper third of the esophageal musculature consists of skeletal muscle and the lower two thirds consist of smooth muscle. The adventitia consists in connective tissue that merges with connective tissue of surrounding structures. Unlike the remainder of the gastrointestinal tract, the esophagus does not have a serosal layer.

The upper esophageal sphincter is formed by the cricopharyngeus muscle along with the inferior constrictors of the pharynx and fibers of the esophageal wall. The lower esophageal sphincter is not a distinct anatomic structure.

M. A. Menezes
Department of Surgery, Universidade Estadual de Londrina, Londrina, Brazil

R. O. Sato
Department of Gastrointestinal Oncology, Hospital de Cancer de Londrina, Londrina, Brazil

F. Schlottmann
Department of Surgery, Hospital Alemán of Buenos Aires, University of Buenos Aires, Buenos Aires, Argentina

F. A. M. Herbella (✉)
Department of Surgery, Federal University of Sao Paulo, Escola Paulista de Medicina, Sao Paulo, Brazil
e-mail: herbella.dcir@epm.br

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Microscopic anatomy of the esophageal wall is further divided for diagnostic and therapeutic purposes to allow a more refined staging and guide endoscopic resection in early esophageal cancer [3, 4]. Thus, mucosa layer is subdivided in: (a) M1—epithelium (defining a carcinoma in situ); (b) M2—lamina propria mucosae; and (c) M3—muscularis mucosae. Submucosal layer is also subdivided in three layers: (a) SM1—upper third of the submucosa; (b) SM2—middle third of the submucosa; and (c) SM3—lower third of the submucosa. Endoscopic resection is suitable for early cancers invading up to the SM1 [5].

Macroscopically, the esophagus is divided in three portions: cervical, thoracic/mediastinal, and abdominal, according to the boundaries of the cavities that it crosses (i.e. the thoracic outlet at the level of the manubrium and the diaphragm). The cervical esophagus lies left of the midline and posterior to the larynx and trachea. The thoracic portion may also be subdivided in: (a) Upper thoracic esophagus—from the sternal notch to the tracheal bifurcation; (b) Middle thoracic esophagus—the proximal half of the two equal portions between the tracheal bifurcation and the esophagogastric junction; and (c) Lower thoracic esophagus—the thoracic part of the distal half of the two equal portions between the tracheal bifurcation and the esophagogastric junction (Fig. 1.1). The upper thoracic esophagus passes behind the trachea and tracheal bifurcation, while the middle and lower thoracic esophagus passes behind the left atrium and then enters the abdomen through the esophageal hiatus of the diaphragm. The abdominal portion may be absent in the case of a hiatal hernia.

Vascularization and Lymphatic Drainage

Esophageal vascularization is shared by small branches from adjacent organs. Arterial blood supply comes from branches of the inferior thyroid arteries, unnamed vessels originating directly from the thoracic aorta, bronchial arteries, inferior phrenic arteries, and left gastric artery. Blood is drained into the inferior thyroid, hemiazygos, azygos and left gastric vein [6].

Anatomy textbooks rarely describe a specific lymphatic drainage of the esophagus. Abundant lymphatics form a dense submucosal plexus. Thoracic lymph nodes are shown in a regular disposition seldom seen in an operation. Gray's anatomy textbook simply describes esophageal lymphatic drainage as "a plexus around that tube, and the collecting vessels from the plexus drain into the posterior mediastinal glands" [7]. Lymph from the cervical and upper-mid thoracic esophagus drains mostly into the cervical, paratracheal and subcarinal lymph nodes, whereas the lower thoracic and abdominal esophagus drains preferentially into the diaphragmatic, paracardial, left gastric, and celiac nodes.

Esophageal Surgical Anatomy

Cervical Esophagus

The access to the cervical esophagus may be obtained through an oblique incision parallel to the medial border of the left sternocleidomastoid muscle or a necklace incision. The former is simpler and the latter allows bilateral access if a complete lymphadenectomy is anticipated. The oblique incision allows access to the esophagus after dividing the platysma muscle (in the subcutaneous) and the deep cervical fascia which will expose the infrahyoide muscles (sternothyroid muscle mainly) that are retracted or divided. These muscles are responsible for larynx depression and its division may impair swallowing and fonation thus preservation is preferred [8]. The esophagus will then be found between the trachea and the carotid sheath [9]. The anterior jugular vein and inferior thyroid vein may occasionally be ligated without consequences. The left recurrent laryngeal nerve lies in the groove between the trachea and esophagus where it is prone to be damaged [10].

A complete cervical lymphadenectomy is best accomplished through a collar incision. This bilateral access allows the resection of the internal jugular nodes below the level of the cricoid cartilage, supraclavicular nodes, and cervical paraesophageal nodes [11] (Fig. 1.2). Muscles are usually spared.

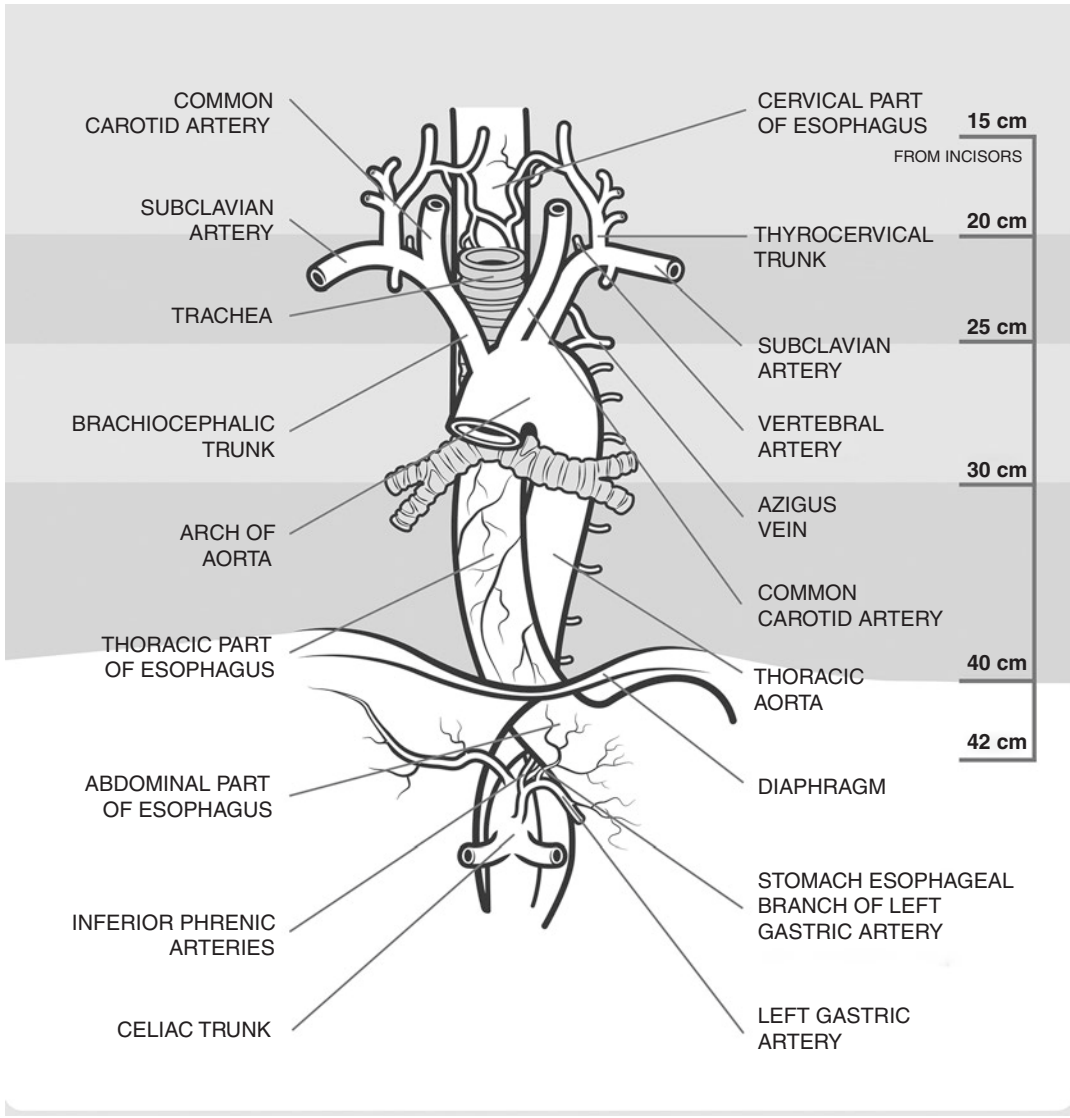


Fig. 1.1 Esophageal anatomy: the three portions of the esophagus and surrounding structures in the posterior mediastinum

Thoracic Esophagus

The access to the thoracic esophagus may be accomplished through a thoracotomy or thoracoscopy. A right approach allows access to the whole esophagus while a left approach is reserved when the interest is in the distal esophagus only. A thoracotomy is usually performed in the lateral position with the surgeon standing in the right side of the patient that allows a panoramic view of the posterior mediastinum after the lung is retracted (Fig. 1.3). A minimally invasive approach brings a restricted view but with a magnified image (Fig. 1.4). Some surgeons advocate the operation to be performed in prone position with putative advantages of lower pulmonary complications and increased number of resected lymph nodes [12] (Fig. 1.5).

The important structures that are intimately related to the thoracic esophagus are the trachea and pericardium ventrally; the azygos vein and right pleura on the right laterally, the spine and

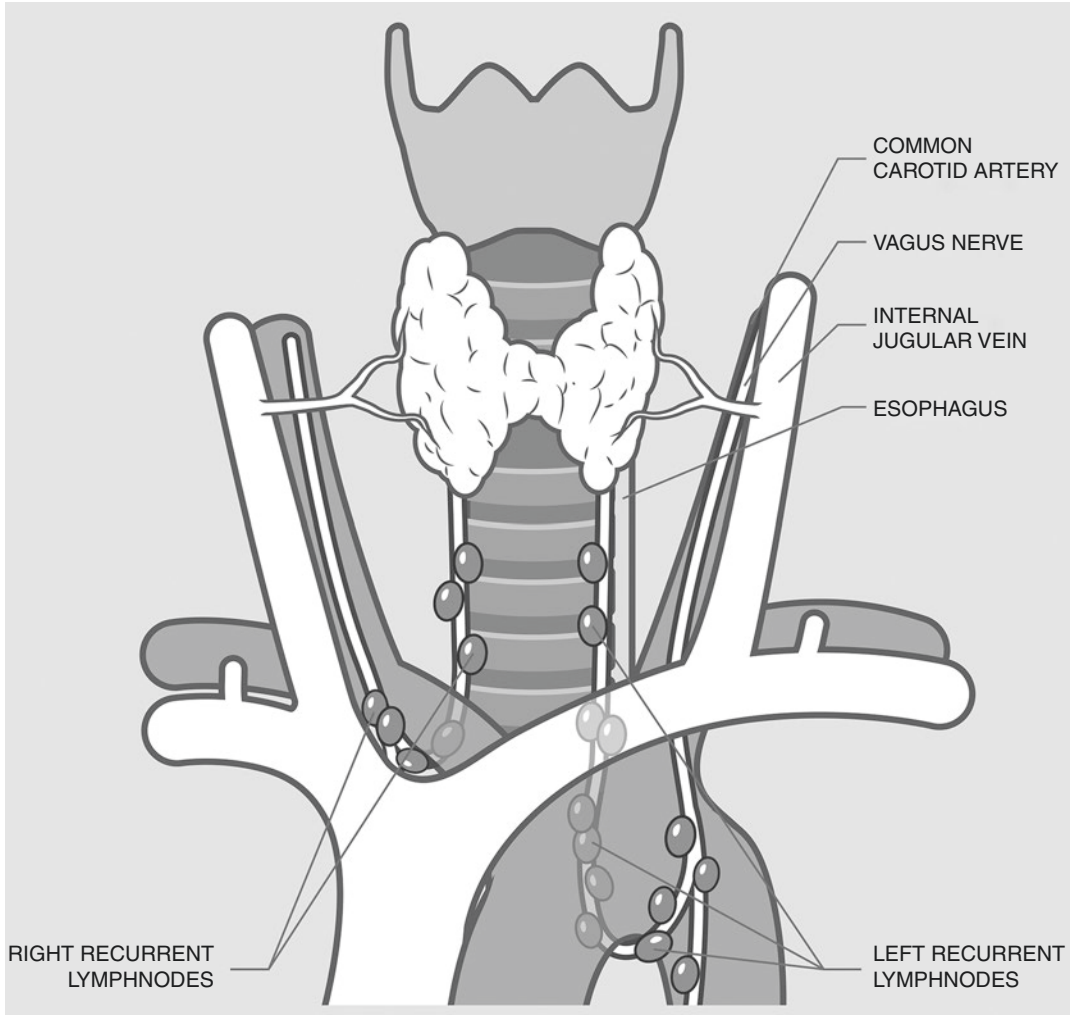


Fig. 1.2 Cervical lymph nodes of interest for esophagectomy and lymphadenectomy

thoracic duct dorsally, and the aorta and left pleura left laterally [13].

The anatomy of the vagus had some relevance at the time when vagal-sparing esophagectomy was attempted in order to prevent morbidity related to vagotomy [14]. Currently, this procedure is seldom performed but a selective preservation of pulmonary vagal branches is proposed [15].

Pleural preservation is desired during a transhiatal esophagectomy to minimize the consequences of thoracic drainage. Pleural lesion may occur during dissection of the mid-thoracic esophagus if a recess of the pleura intervenes between the esophagus and the azygos vein on the right side below the pulmonary veins. However, the pleura is more commonly injured during the dissection of the distal left esophagus where they are in close contact [10].

The azygos system anatomy is of interest during an esophagectomy since the arch of the azygos vein is divided to allow a better exposure of the upper thoracic esophagus, and these veins are resected during an en-bloc esophagectomy [16]. Some authors, on the other side, believe the resection of the azygos system is not considered essential since it does not affect the number of retrieved lymph nodes [17]. Variations of the azygos system

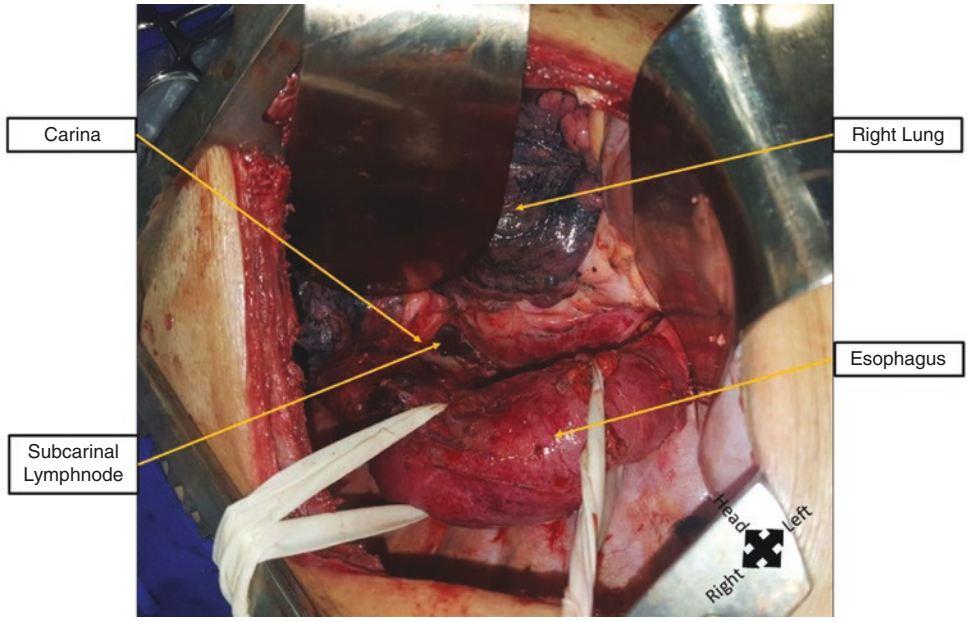


Fig. 1.3 Right thoracotomy. The access through the intercostal space limits the view and access to the esophagus in the posterior mediastinum. An adequate retraction of the lungs medially is mandatory

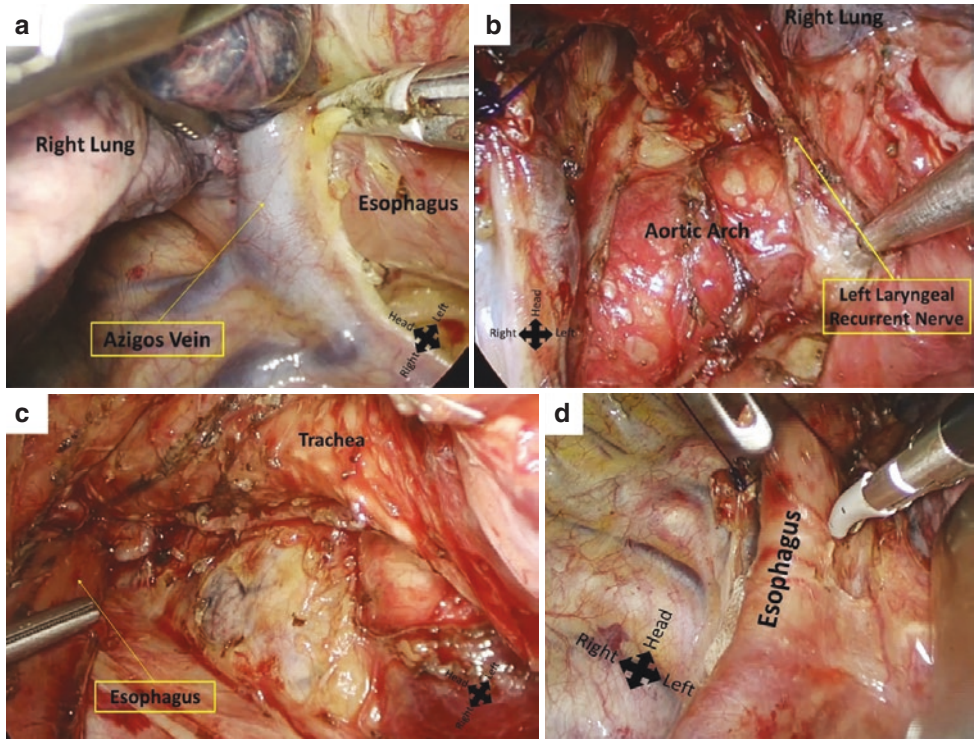


Fig. 1.4 Right thoracoscopy in lateral position. Minimally invasive surgery allows a magnified but restricted operative view but camera freedom of movement allows visualization of the complete thoracic cavity: upper part where the azigos vein crosses the esophagus (**a**) area of the aortic arch where left laryngeal nerve lymph nodes are located (**b**), trachea (**c**), the whole extension of the esophagus (**d**)

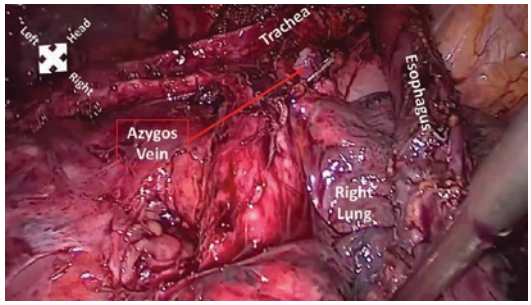


Fig. 1.5 Right thoracoscopy in prone position. The prone position has the advantage of removing the lungs from the operative view and allows good access to the respiratory tract to perform lymphadenectomy of peritracheal lymph nodes. The laryngeal recurrent nerves are; however, in an obstructed view

are uncountable and related to the origin of the veins or the communication between the left and right side systems. However, the clinical importance of these variations is negligible since they can be promptly recognized during an esophagectomy and comprise small caliber vessels that can be easily ligated without any consequences [10].

The recurrent laryngeal nerve has a thoracic course and can be injured during the dissection of the lymph nodes present along its course (node stations 2 and 4) [18]. The right recurrent nerve originates at the origin of the right subclavian artery behind the sternoclavicular joint, loops around the artery and ascends to the neck. The left recurrent nerve originates at the inferior border of the aortic arch, them it loops around the aorta and ascends to the neck [19]. Anatomic variations are uncommon. Non-recurrence may occur in 10% of the cases but since the nerve does not have a thoracic course in these cases, it is automatically protected from injury [10].

The thoracic duct origins in the cisterna chyli in the abdomen, ascends to the posterior mediastinum, to the right of the midline, between the descending thoracic aorta on the left and the azygos vein on the right. The duct inclines to the left, enters the superior mediastinum, and ascends toward the thoracic inlet along the left edge of the esophagus. The thoracic duct usually ends at the junction of the left subclavian and internal jugular veins [20]. There are commonly major anatomical variations that may lead to intraoperative injury during an esophagectomy [10]. The intraoperative identification of the injury and the duct itself may be difficult. Therefore, mass ligation of the duct including all tissue between the aorta, spine, esophagus, and pericardium is recommended in cases of suspect lesion of the duct [21]. Mass ligation is preferred over identification and individual ligation since duplication or plexiform ducts are common [10].

A proper lymphadenectomy is an essential part of an oncologic esophagectomy [22]. Thus, the knowledge of the anatomy of the lymph nodes that drain the esophagus is mandatory. Unfortunately, anatomy textbooks frequently show a regular disposition of nodes (Fig. 1.6) not useful for surgeons. In addition, there is no standard classification and nomenclature of mediastinal lymph nodes (Table 1.1), and the number and location of lymph nodes is commonly erratic [23].

Abdominal Esophagus

The esophagus has a constant and short course in the abdomen that is familiar to surgeons used to laparoscopic surgery of benign esophageal disorders at the esophagogastric junction [24].

A 2 or 3-field lymphadenectomy will include the lymph nodes of the upper abdomen [25] in a similar fashion to the D2 lymphadenectomy for gastric cancer [26] (Fig. 1.6).

Anatomy for Esophageal Replacement

Alimentary tract reconstruction after an esophagectomy is regularly accomplished with a gastric tube as a graft. However, the colon may be used in particular situations [27, 28]. The vascular anatomy of these organs is therefore important to establish an adequate blood supply to the replacing organ.

For a gastric tube, the left gastric artery and coronary vein are divided, as well as the short gastric vessels. The blood supply will be provided by the right gastric artery and the right gastroepiploic artery [29] (Fig. 1.7).

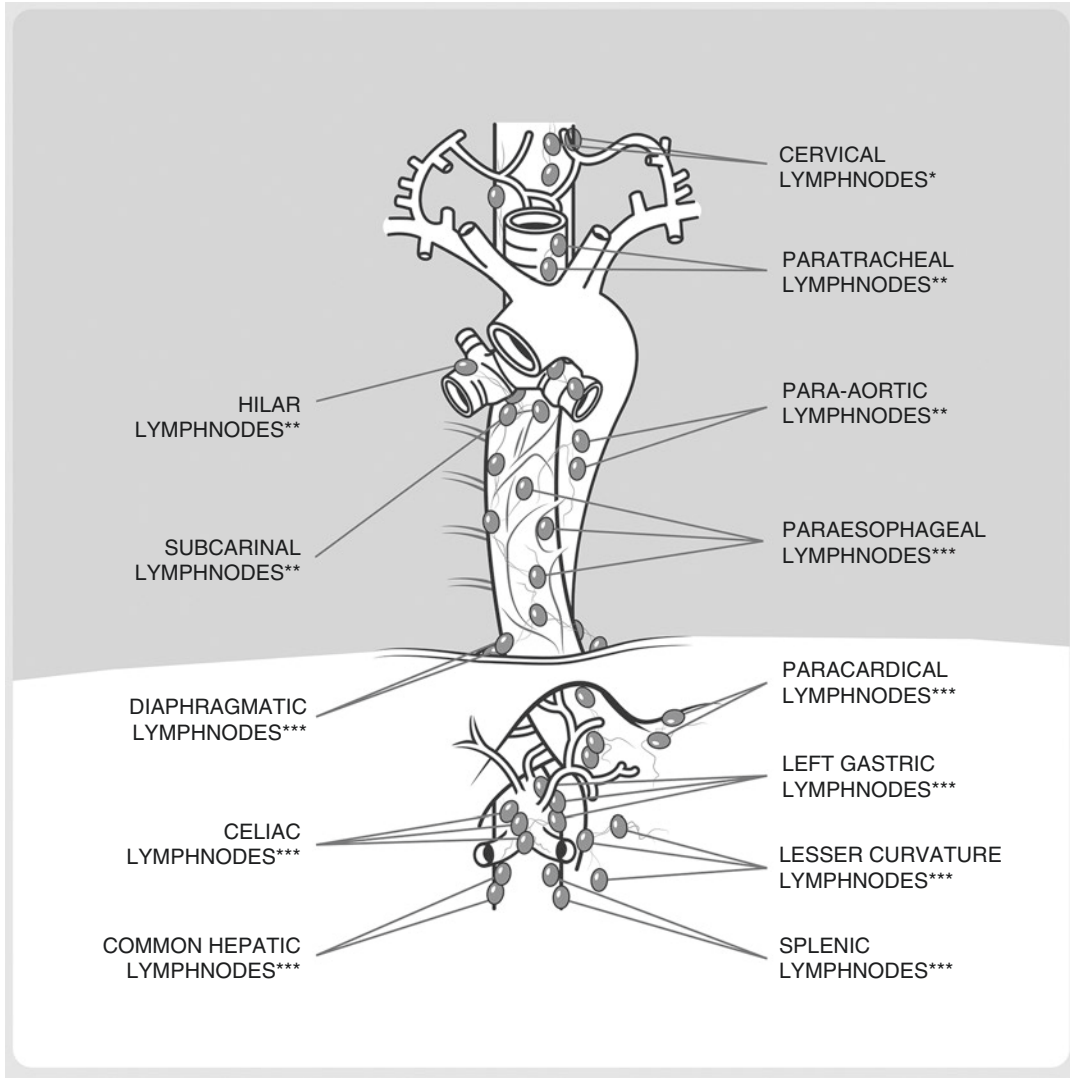


Fig. 1.6 Lymph nodes of interest to esophagectomy and lymphadenectomy. The exuberant lymphatic drainage of the esophagus may lead to metastasis in cervical (*), thoracic (**) and abdominal (***) periesophageal lymph nodes

For a colonic interposition, diverse segments of the colon can be used (Table 1.2). The most common reconstruction options are the left colon, with the ascending branch of the left colic vessels [28, 30], and the right colon with the middle colic vessels [31] or even with the left colic vessels [32] (Fig. 1.8). Since a segment of transverse colon is need irrespective if right or left colon is used, vascularization of the graft is dependent on anastomosis between the different colic pedicles. In a series of mesenteric arteriograms, the marginal artery in the right colon was present in only 30% of the cases, while in the left colon it was present in all cases [33]. Thus, the blood supply of the right colon is less reliable than that of the stomach and left colon [34]. Some surgeons prefer to have a preoperative angiography in order to identify the anatomy of the arteries and the continuity of the marginal artery [35] while others do not consider it necessary [36].

The replacing organ may reach the neck through different routes: posterior mediastinum, anterior mediastinum, transpleural (rare) and subcutaneous (rare). There are controversial

results on the length of the anterior (retrosternal) as compared to the posterior route [37–39]. The anterior path, however, is more constricted at the level of the thoracic inlet [40].

Table 1.1 Mediastinal lymph nodes classification according to a Japanese Society of Esophageal Disease and American Joint Committee for Cancer and their correlations

Japanese Society for Esophageal Disease	American Joint Committee for Cancer
102—Deep cervical	1—Highest mediastinal
105—Upper thoracic esophaggeal	2—Upper paratracheal
106—Thoracic paratracheal	2—Upper paratracheal 4—Lower paratracheal
107—Bifurcation	7—Subcarinal
108—Middle thoracic paraesophageal	8M/8Lo—Paraesophageal
109—Pulmonary hilar	8M—Paraesophageal
110—Lower thoracic paraesophageal	8Lo—Paraesophageal
111—Diaphragmatic	15—Diaphragmatic
112—Posterior mediastinal	9—Pulmonary ligament

Esophageal Radiologic Anatomy

The development of clinical imaging has allowed surgeons to better stage patients with esophageal cancer and plan the surgical approach. The old barium esophagram has been replaced by newer studies.

Endoscopic Ultrasound

Endoscopic ultrasound allows visualization of the esophageal wall and adjacent structures. Although microscopic details can be obtained, the range of this technique is limited to a few centimeters adjacent to the esophageal wall. The sonographic image distinguishes five distinct layers (Fig. 1.9): the innermost layer with increased echogenicity and a thin hypoechoic layer immediately deep to it correspond mainly to the mucosa and partly to the muscularis mucosae, and that the next echogenic layer corresponds to the submucosa. The fourth hypoechoic layer is the muscularis propria layer and the outermost

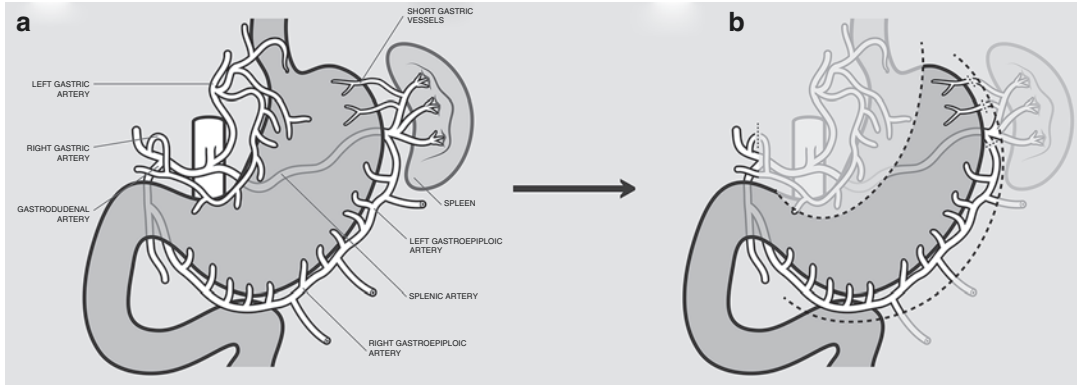


Fig. 1.7 Vascular anatomy of the stomach of interest to esophageal replacement (**a**). The gastric tube is supplied by the right vessels (**b**)

Table 1.2 Relationship between blood supply, the segment of the colon used for esophageal replacement and type of peristalsis

Arterial supply	Colon conduit	Peristalsis
Ileocolic artery	Ascending + transverse	Antiperistalsis
Right colic artery	Cecum + ascending	Isoperistalsis
	Ascending + transverse	Antiperistalsis
Middle colic artery	Cecum + ascending + transverse	Isoperistalsis
	Ascending + transverse	Antiperistalsis
Left colic artery	Transverse + descending	Isoperistalsis

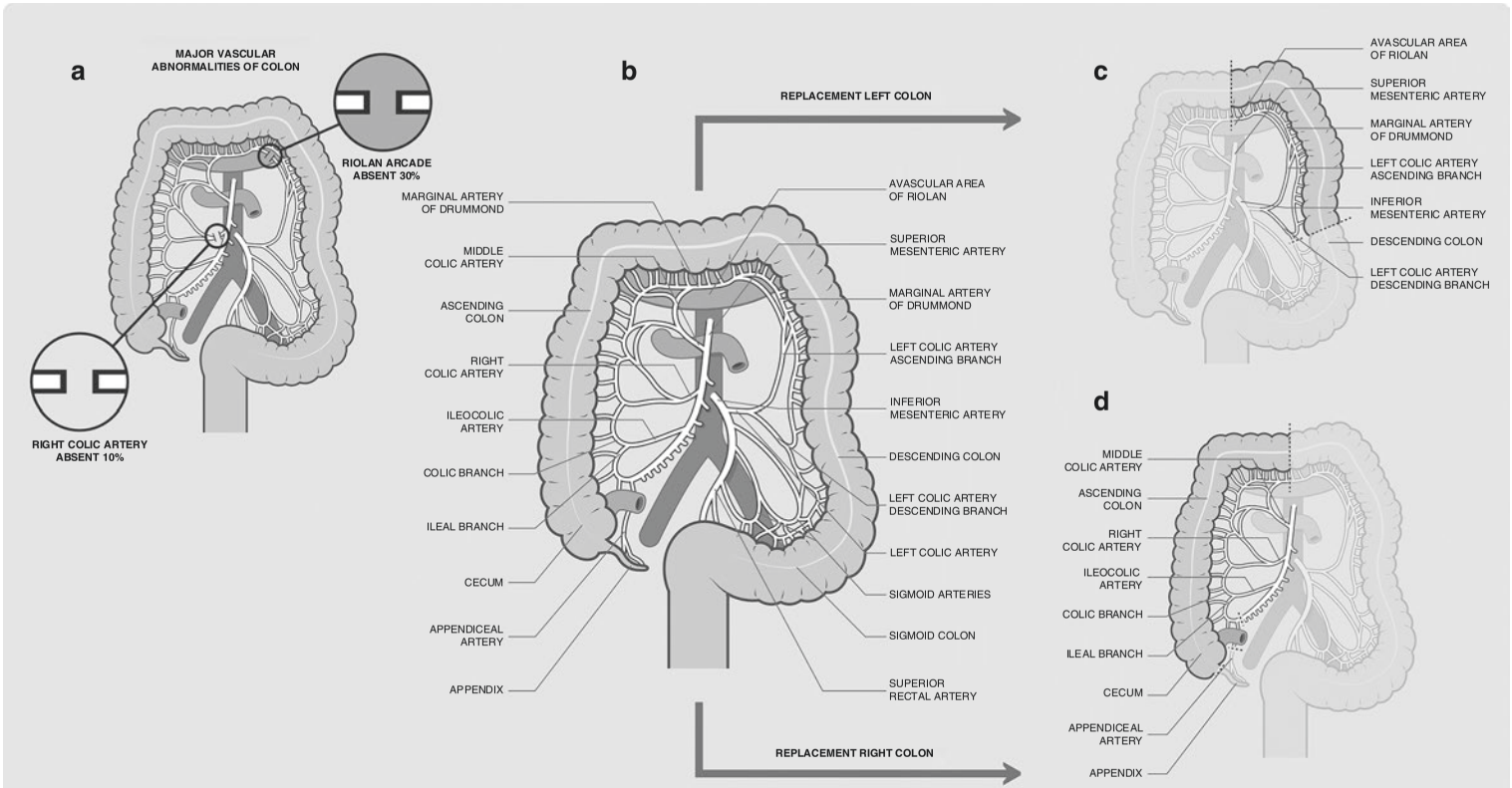


Fig. 1.8 Vascular anatomy of the colon of interest to esophageal replacement. A patent arcade communicating the superior and inferior mesenteric vessels is mandatory to supply the graft. This communication is absent in some cases but it can be tested during the operation (**a**). The vessels that supply the left or right colon used as a graft are represented in **b**, **c**, and **d**

echogenic layer is the adventitia with fat appendage [41]. Lymph nodes can also be identified by endoscopic ultrasound [42].

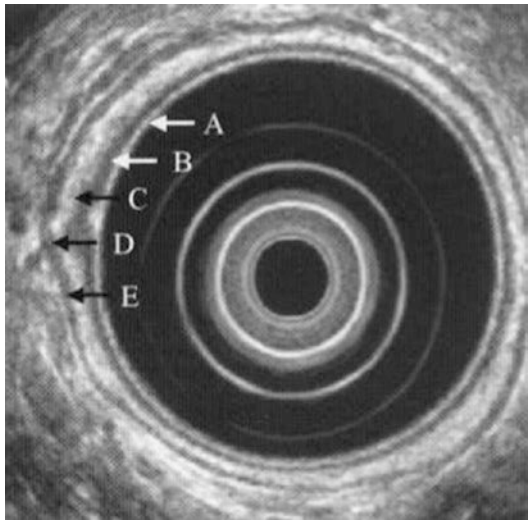


Fig. 1.9 Endoscopic ultrasound of the esophagus with five distinct layers: (**a**) mucosa, (**b**) muscularis mucosae, (**c**) submucosa, (**d**) muscularis propria, and (**e**) adventitia

Computed Tomography

Computed tomography of the neck, chest and abdomen allows high quality imaging of the esophagus and 3D reconstruction [43] (Fig. 1.10). The detection of lymph nodes by computed tomography correlates well to anatomic findings [23, 44].

Magnetic Resonance

Dedicated techniques of magnetic resonance protocols increased esophageal anatomy visualization as compared to computed tomography. Magnetic resonance is able to detect individual layers of the esophageal wall, the thoracic duct, a connective tissue layer attaching the esophagus to the anterior wall of the aorta, and a fascial plane passing between layers of the right and left parietal pleura posterior to the esophagus [45]. Some surgeons believe the study of these planes and layers allows a more detailed dissection of the esophagus in order to preserve nerves and retrieve lymph nodes more efficiently [13].

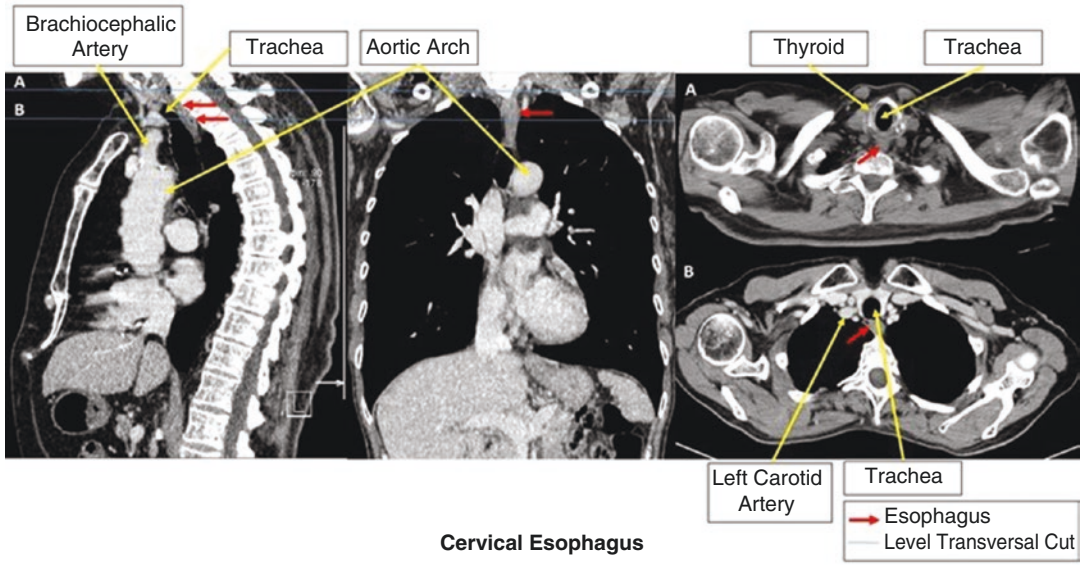
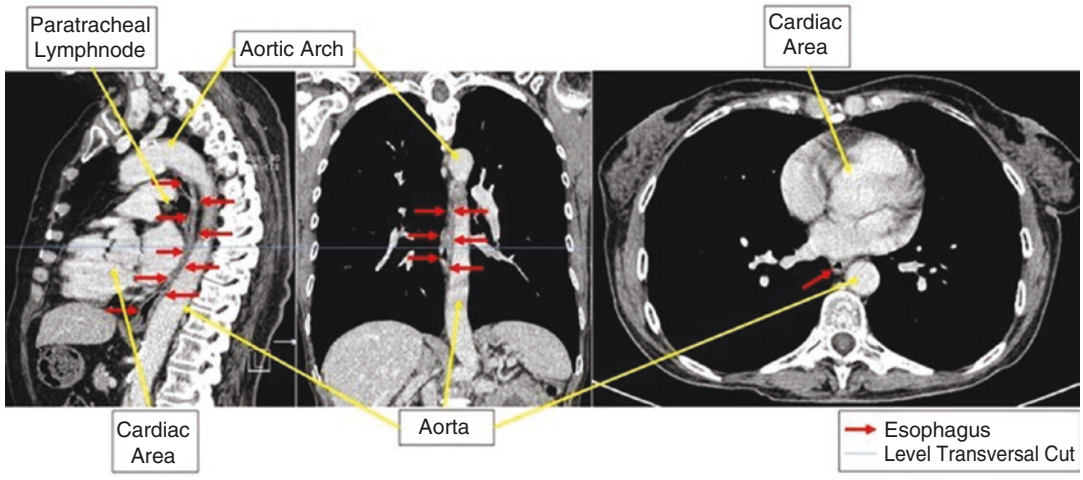
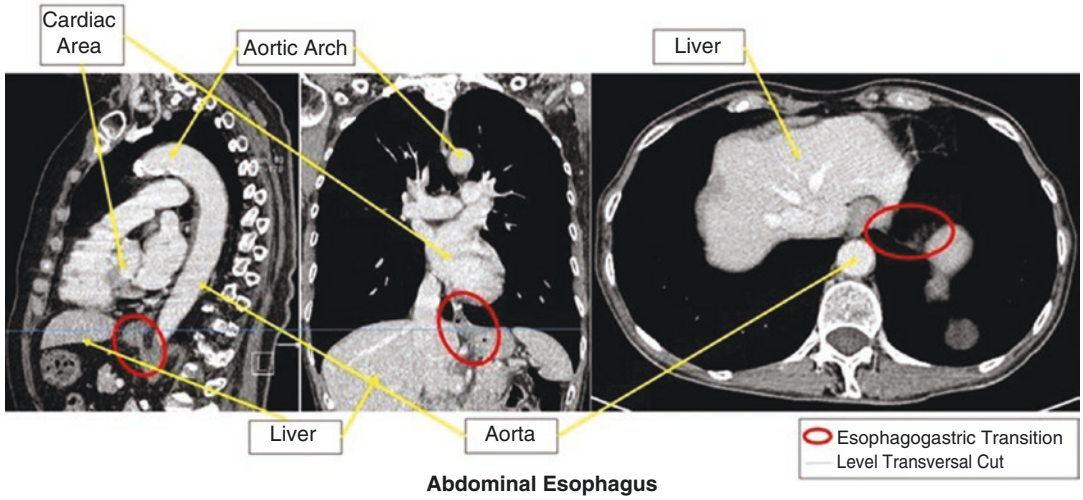


Fig. 1.10 Computerized tomography scans of the esophagus and surround structures. Tomography has a limited differentiation of tissues in the mediastinum as compared to magnetic resonance but the visualization of the esophagus and lymphnodes are adequate for clinical decisions



Thoracic Esophagus



Abdominal Esophagus

Fig. 1.10 (continued)

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2 Esophageal Squamous Cell Cancer: Pathogenesis and Epidemiology

Daniel Tong and Simon Law

Introduction

Esophageal cancer is a disease of dismal prognosis. The two major histologic types of tumors, squamous cell carcinoma and adenocarcinoma, differ substantially in epidemiology, and pathogenesis. Squamous cell carcinoma remains the main cell type worldwide and most are found in Eastern populations. The reported 5-year survival rates for esophageal cancer are 21% in China [1], 20% in the United States [2], 12% in Europe [3], and <5% in places where resources are limited [4, 5]. The cancer is characterized by late presentation and rapidly fatal course. This makes study on modifiable risk factors for esophageal cancer particularly important in the context of disease prevention. The present chapter addresses the epidemiology and pathogenesis with emphasis on esophageal squamous cell carcinoma (ESCC).

Epidemiology

Esophageal cancer is the eighth most common cancer worldwide and the sixth most common cause of cancer death [6, 7]. ESCC remains the predominant histologic type worldwide with an estimated 398,000 new cases in 2012, representing 87% of all esophageal cancer [8]. There is significant variation of incidence among different geographic regions and various ethnic groups. In Asian countries, it is commonly found in the "*Asian esophageal cancer belt*", bounded by eastern Turkey and east of Caspian Sea through northern Iran, northern Afghanistan, and southern areas of the former Soviet Union, such as Turkmenistan, Uzbekistan, and Tajikistan, to northern China and India. In high incidence areas, the occurrence of esophageal cancer is 50–100-fold higher than that in the rest of the world. Examples of such high-incidence areas include Linxian province in China, Golestan province in Iran, Western Kenya south to Malawi, the Eastern Cape province of South Africa, Calvados in France, Southern Brazil and Uruguay.

In China, esophageal cancer is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death. The age-standardized incidence rate of esophageal cancer is 27.4 per 100,000, compared to 10 in Japan, 7.9 in northern Europe, 7.6 in western Europe, 5.8 in North America, and 5.5 in Australia/New Zealand [9]. The crude age-adjusted mortality is up to 140 per 100,000 and is one of the most common causes of cancer death in China. Generally, incidence rates are higher in rural areas than in urban areas. Henan, Hebei, and Shanxi have the highest incidence rates in the world. Cixian has an incidence rate 18 times that of Beijing or Shanghai.

D. Tong · S. Law (✉)
Division of Esophageal and Upper Gastrointestinal Surgery, Department of Surgery,
The University of Hong Kong, Queen Mary Hospital, Hong Kong, China
e-mail: slaw@hku.hk

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Esophageal cancer most commonly presents in the sixth and seventh decades of life. In most countries, ESCC is a male-predominant disease. The trend of esophageal cancer remains steady in most countries in recent decades. The disease is rare before age of 40 and incidence peaks at 70–80 years of age according to National Central Cancer Registry of China [10].

Pathogenesis

Alcohol and Smoking

Tobacco and alcohol intake are the two major risks factors for esophageal squamous cell carcinoma (Table 2.1). Smoking is regarded by the International Agency for Research on Cancer (IARC) as a cause of esophageal cancer [11]. Compared to non-alcohol drinkers, the risk of esophageal squamous cell carcinoma increases by 38%, 260% and 550% among those who drink alcohol 1–1.5 L/day, 1.5–6 L/day and >6 L/day, respectively [12, 13]. Alcohol and smoking have a synergistic effect on the risk of ESCC. The mechanism of this synergistic effect is well studied. Alcohol damages the cellular DNA by decreasing metabolic activity within the cell and therefore reduces detoxification function and promotes oxidation [14]. Alcohol can act as a solvent for fat-soluble carcinogens such as aromatic amines, nitrosamines, polycyclic aromatic hydrocarbons, phenols, and aldehyde. Therefore, these substances from tobacco can easily diffuse to the esophageal tissue. A recently published meta-analysis showed that the combined effect of drinking and smoking doubled the sum of their effects individually [15]. In low- or medium-incidence populations including Europe and the United States, ESCC is largely attributed to smoking and alcohol and the incidence rates are three to four times higher in men than in women [16]. In the United States, United Kingdom, and France, population attributable risks of 74–89% have been reported for squamous cell carcinoma, based on smoking and consumption of alcohol, fruit, and vegetables [17–19]. Similar studies in high incidence countries in Asia such as China estimate that 46% esophageal cancer death is attributable to the combined effect of alcohol, smoking, low fruit and vegetable intake [20, 21].

Table 2.1 Etiology factors for squamous cell esophageal cancer

Factor	Contribution
Alcohol	+++
Smoking	+++
Diet related	
Deficiencies of fresh green vegetables, fruits and vitamins	+
N-nitroso containing food (e.g. pickled vegetables)	+
Chewing betel nut and mate drinking	+
Hot beverages	+
Fungal toxin	+
Infection	
Human papilloma virus	±
Pre-malignant conditions	
History of aerodigestive malignancy	+++
History of radiation to mediastinum	+
Achalasia	+
Lye corrosive stricture	+
Genetic factors	
Alcohol dehydrogenase deficiency	++
Tylosis	+
Plummer-Vinson syndrome	+
Others	
Low socioeconomic class	+

Genetic Factors

Genetic predisposition may be important in the pathogenesis of ESCC. Genome-wide association studies have demonstrated a high heritability of ESCC when compared to other cancers [22], and there is an increased risk of ESCC in people who have a positive family history [23–25]. Mitochondrial studies have proved historical population migrations from central/northern to southern-eastern China; the two regions share the same high risk of ESCC and yet environmentally they are quite different [26]. Tylosis is a familial esophageal cancer syndrome inherited as an autosomal dominant trait. It has also been reported to be associated with genetic mutations in RHBDF2 [27]. These observations suggest

that hereditary factors play a part in ESCC pathogenesis. Genetic polymorphism is important in individuals with chronic alcohol consumption [28]. Polymorphisms in ADH1B, ADH7, and ALDH2 are known to alter ethanol metabolism [27, 28]. Approximately 36% of East Asians show a physiologic response to drinking that includes facial flushing, nausea, and tachycardia [28]. This facial flushing response is predominantly related to an inherited deficiency in the enzyme aldehyde dehydrogenase 2 (ALDH2). Alcohol is metabolized to acetaldehyde by alcohol dehydrogenase and the acetaldehyde is in turn metabolized by ALDH2 to acetate. Two main variants for ALDH2 exist, resulting from the replacement of glutamate with lysine at position 487. Only individuals homozygous with the glutamate allele have normal catalytic activity. Homozygotes with the lysine alleles have no detectable activity, while heterozygotes with Glu/Lys alleles have much reduced ALDH2 activity. The inability to fully metabolize acetaldehyde results in its accumulation in the body leading to the facial flushing and unpleasant side effects. Lys/Lys homozygotes cannot tolerate much alcohol because of the intensity of the side effects, and so paradoxically they do not have increased risk because they simply would not consume a significant amount of alcohol. Individuals who are Glu/Lys heterozygotes may become habitual drinkers because they could become tolerant to the side effects of alcohol and yet they have suboptimal catalytic activity and thus the acetaldehyde accumulates. These are the individuals most susceptible to the carcinogenic effects of alcohol consumption, which is related to acetaldehyde causing DNA damage and other cancer-promoting effects [29]. A simple questionnaire that elicits the history of a flushing response can be useful in identifying at-risk individuals. They could be advised against drinking or to undergo screening endoscopy, and the risk of developing cancer may be reduced or an earlier diagnosis could be possible [30].

Diet and Environment

In Asian countries, dietary and environmental factors certainly play a role in the development of ESCC. Studies have investigated the effects of dietary patterns, specific food and nutrients on the disease [31, 32]. Nitrosamines and their precursors such as nitrate, nitrite, and secondary amines, are found in pickled vegetables, which in turn have been shown to increase risk [33]. Nutritional depletion of certain micronutrients, particularly vitamins A, C, E, niacin, riboflavin, molybdenum, manganese, zinc, magnesium selenium, as well as fresh fruits and vegetables, together with an inadequate protein intake, predisposes the esophageal epithelium to neoplastic transformation [34]. Lack of fresh fruit and vegetables is associated with increased risk of ESCC [35]. A meta-analysis comprising several prospective studies showed that eating fruits and vegetables significantly reduced ESCC risk [36]. The Nutrition Intervention Trial conducted in Linxian county in China showed that consumption of vitamin B2 and nicotinic acid decreased the incidence of esophageal cancer by 14%, while beta-carotene, vitamin E, and selenium intake could reduce esophageal cancer mortality by 17% in patients less than 55 years old [37].

Consumption of red meat, processed meat, and hot mate were shown to be associated with increased risk of ESCC. A meta-analysis showed that the cancer risk was 57% higher in people who consumed a large amount of red meat and 55% higher in people who took a large amount of processed meat [38]. Mate drinkers have a 60–260% increased ESCC risk compared to non-drinkers in South American countries [39, 40].

Change in specific dietary habits, such as replacing traditional methods of food preservation and storage with refrigeration, together with consumption of vitamin-rich food, may have produced a drop in incidence rates in certain areas of China, especially in urban cities such as Shanghai [41]. Consumption of hot food and beverages is associated with an increased risk of esophageal cancer, particularly squamous cell cancer [42]. This is also evident in Chinese population [43]. It was found that green tea drinking per se is not associated with increased risk of ESCC but drinking hot or extremely hot green tea is.

Infection

The role of human papillomaviruses (HPV) in ESCC is controversial. The HPV and certain fungi belonging to the genera *Fusarium, Alternaria, Geotrichum, Aspergillus, Cladosporium, and Penicillium* are infective agents found to be associated with esophageal cancer as demonstrated in some studies [44, 45]. However, several recent studies suggest HPV plays little role in ESCC etiology and therefore HPV vaccines may not be beneficial in cancer prevention [46–48].

Premalignant/Neoplastic Condition

Patients with other aerodigestive malignancies have a particularly high risk of developing ESCC, presumably because of exposure to similar environmental carcinogens and the phenomenon of "field cancerization." Using esophageal cancer as the index tumor, multiple primary cancers were found in 9.5% of patients, of whom 70% were in the aerodigestive tract [49]. The overall incidence of synchronous or metachronous esophageal cancer in patients with primary head and neck cancer is estimated to be 3% [50].

Diseases that are known to predispose to esophageal cancer are few. The risk from achalasia is estimated to be 7–33-fold, but symptoms of achalasia are present for an average of 15–20 years before the emergence of cancer [51]. Other diseases include lye corrosive strictures, Plummer-Vinson syndrome, tylosis and celiac disease.

Other Factors

A low socioeconomic class is associated with increased risk of ESCC. It is believed to be the interplay among many factors, such as poor nutritional status, a diet lacking in fresh food, fruit and vegetables, and also poor oral hygiene and tooth loss. A recent study showed that tooth brushing exerts protective effects against ESCC and tooth loss is associated with increased risk of ESCC [52]. A similar phenomenon is not only found in Asia but also in South America and Europe [53]. These findings, however, should be interpreted carefully as poor oral hygiene can also be associated with smoking and drinking habit.

Prevention

ESCC is notorious for its poor prognosis; in its early stage it is asymptomatic and the majority of patients are diagnosed at advanced stage. The disease also tends to spread early compared to the equivalent depth of invasion for other gastrointestinal tract cancers. Identifying modifiable risk factors allows potential prevention and screening at high-incidence regions. This will facilitate early diagnosis and improve prognosis.

In order to reduce the risk of ESCC, people should avoid risk factors and change to a healthy life-style. These include quitting smoking and alcohol drinking, consumption of more fresh vegetables and fruits, and reducing exposure to carcinogens such as food containing nitrites or nitrosamine.

For early detection and disease screening, there is no current international consensus, probably because of the substantial geographic variations in prevalence and concerns on cost-effectiveness. Certain parts of China have developed screening strategies since the 1970s. Balloon cytology with smears, liquid-based balloon cytology, occult blood detection and endoscopic examination are the techniques for esophageal cancer screening. Chromoendoscopic examination using Lugol's iodine solution has been shown to be effective in Korea, Japan, and China for the screening of esophageal cancer. These screening strategies and techniques, however, remain less applicable in low incidence regions.

Conclusion

ESCC is a fatal disease that imposes a significant burden on the health care system, especially in high prevalence countries. Studying the epidemiology and pathogenesis allows health education, nutritional intervention and implementation of screening policy in high-risk areas.

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3 Esophageal Adenocarcinoma: Pathogenesis and Epidemiology

Francisco Schlottmann and Marco G. Patti

Epidemiology

Esophageal cancer is the eighth most common cancer worldwide, with an estimated 456,000 new cases and 400,000 deaths in 2012 [1]. About 87% of all esophageal cancers globally are squamous cell carcinomas (SCC), with the highest incidence rates in populations within South-Eastern and Central Asia, Eastern Africa, and South America. Only 11% of all esophageal cancers are esophageal adenocarcinomas (EAC), with an elevated burden seen in Northern and Western Europe, Oceania, and Northern America (Figs. 3.1 and 3.2) [2]. In these regions, the continuing declines in incidence rates of SCC are offset by rapid increases in the incidence of EAC since the late 1980s, surpassing the rate of SCC since the early 1990s [3]. Over the past 40 years, the incidence of EAC has increased more than sixfold in Western countries [4]. EAC rates are substantially higher in men than in women, with a male to female ratio of 8.5 in Northern America [2].

The increase incidence of EAC has been attributed to the rising prevalence of obesity and gastroesophageal reflux disease (GERD). In fact, the strongest known risk factor for EAC is GERD, together with its more severe manifestation, Barrett's esophagus (BE). GERD affects an estimated 20% of the population in the US, and its prevalence is increasing worldwide [5]. While medical therapy have shown excellent results in controlling GERD symptoms, they have not averted the malignant complications of this disease. Increases in the prevalence of overweight and obesity have paralleled rises in the incidence of EAC in most countries. Although obesity also favors the development and severity of GERD, it has been shown to act as an independent risk factor for EAC, with a 52% increase in risk for every five units in body mass index [6, 7].

The total number of new EAC cases is expected to increase substantially. The United States and The United Kingdom are predicted to have the largest annual number of EAC diagnoses by 2030, with about 15,000 new cases in the US and about 8,600 cases in The United Kingdom. By 2030, one in 100 men may be diagnosed with EAC in The United Kingdom and The Netherlands during their lifetime (Table 3.1) [8].

F. Schlottmann (✉)
Department of Surgery, Hospital Alemán of Buenos Aires, University of Buenos Aires, Buenos Aires, Argentina

M. G. Patti
Department of Medicine and Surgery, University of North Carolina, Chapel Hill, NC, USA

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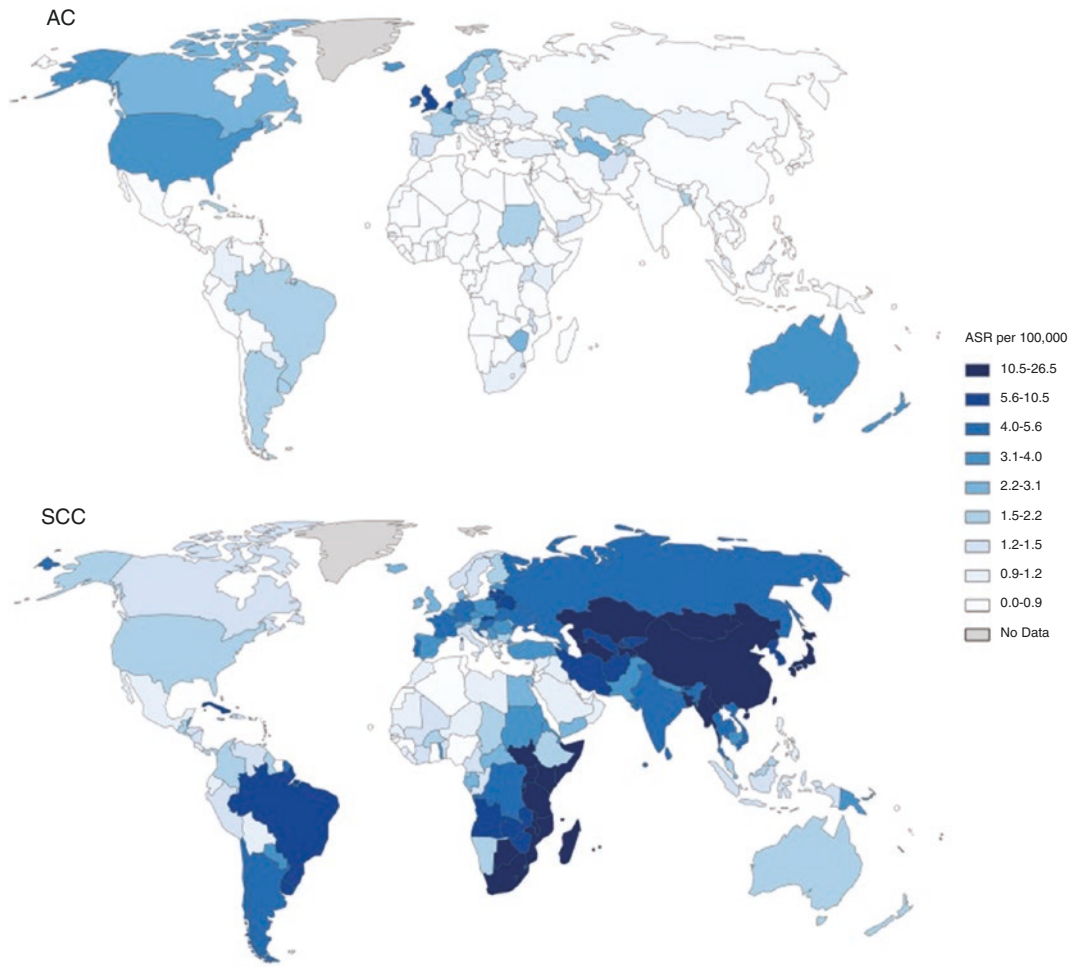

Fig. 3.1 Age standardized incidence rate (ASR) per 100,000 population of esophageal adenocarcinoma and squamous cell carcinoma in men (Obtained with permission from "Global incidence of oesophageal cancer by histological subtype in 2012. Gut 2015.")

Pathophysiology: From GERD to Barrett's Esophagus

About 10–15% of patients with GERD will develop BE [9]. BE has been traditionally defined as the presence of at least 1 cm of metaplastic columnar epithelium that replaces the stratified squamous epithelium normally lining the distal esophagus. Currently, the presence of intestinal metaplasia—columnar epithelium with goblet cells—is also needed for the diagnosis of BE in the US [10]. The reason that intestinal metaplasia is mandated in the definition of BE is related to the higher risk of developing cancer in columnar epithelium containing goblet cells as compared to columnar epithelium without intestinal metaplasia [11, 12].

The transformation of normal esophageal squamous mucosa into a simple columnar epithelium is thought to be due to the chronic injury produced by repeated reflux episodes. In fact, in patients with GERD, symptom duration has been shown to be a risk factor for the presence of BE. Lieberman [13] showed that compared with patients with GERD symptoms for less than 1 year, the odds ratio for BE in patients with GERD symptoms for 5 years was 3.0 and increased to 6.4 in patients with symptoms for

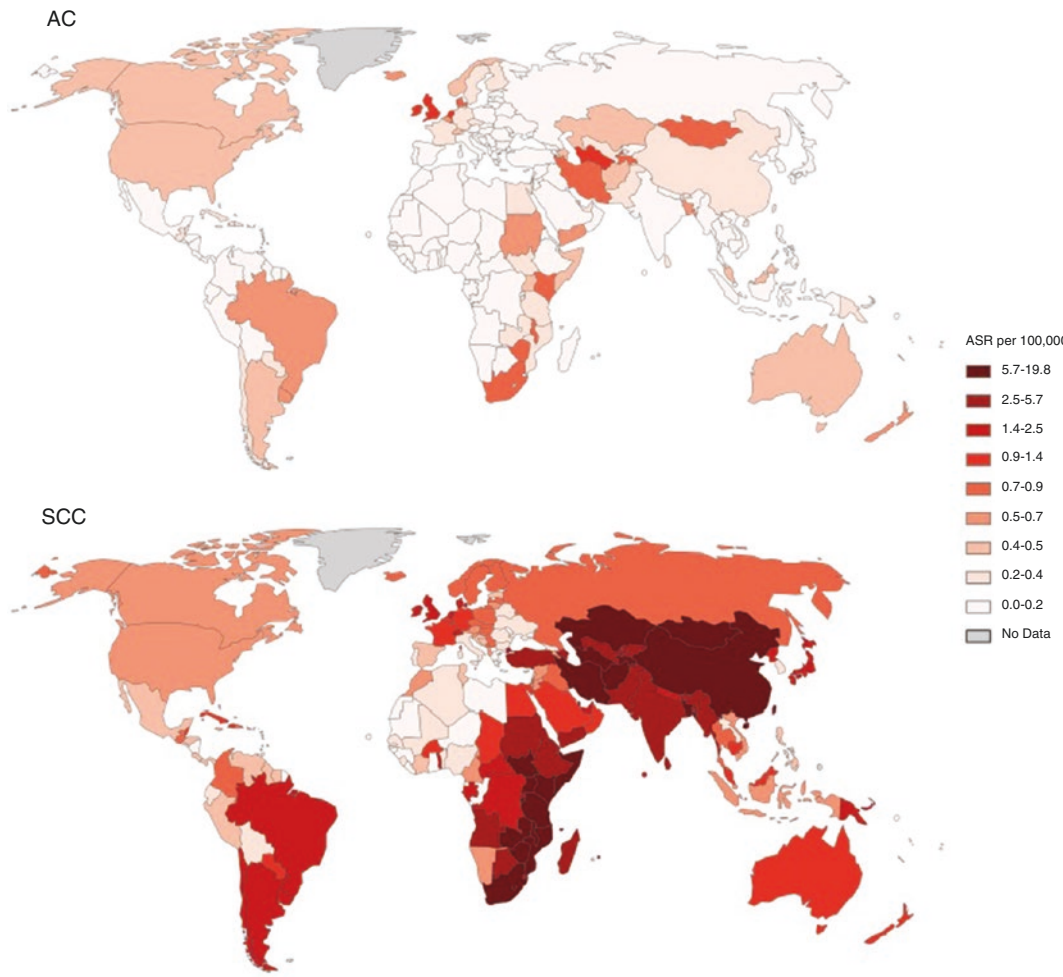

Fig. 3.2 Age standardized incidence rate (ASR) per 100,000 population of esophageal adenocarcinoma and squamous cell carcinoma in women (Obtained with permission from "Global incidence of oesophageal cancer by histological subtype in 2012. Gut 2015.")

Table 3.1 Estimated number of new esophageal cancer cases in 2030, as compared to 2005

	Population (million)		EAC		SCC		Total	
Country	2005	2030	2005	2030	2005	2030	2005	2030
Australia	19.9	28.5	537	1420	486	706	1023	2126
Canada	32.2	40.4	770	2043	462	379	1233	2423
France	61.1	68.0	1193	2863	3116	1930	4309	4793
Japan	126.8	120.1	670	1037	13,646	20,084	14,316	21,121
Netherlands	16.3	17.6	875	2652	514	714	1389	3366
UK	60.1	70.1	4278	8603	2708	3773	6986	12,376
US	277.5	316.8	8167	15,081	4736	4976	12,903	20,057

Data extracted from "Predicting the Future Burden of Esophageal Cancer by Histological Subtype: International Trends in Incidence up to 2030. Am J Gastroenterol 2017"
EAC Esophageal adenocarcinoma, *SCC* Squamous cell carcinoma, *UK* The United Kingdom, *US* The United States

more than 10 years. Interestingly, columnar mucosal metaplasia is also seen in the esophageal remnant in patients with a gastric pull-up following an esophagectomy, where the reflux of gastric contents into the residual esophagus is common because there is no lower esophageal sphincter. Oberg et al. [14] reported that 46.9% of the patients had metaplastic columnar mucosa within their cervical esophagus following an esophagectomy, and the length of that metaplastic mucosa was significantly correlated with the degree of the esophageal acid exposure. O'Riordan et al. [15] reported similar findings with 50% of patients developing columnar metaplasia in the remnant esophagus, with the duration of reflux being the most important factor influencing that transformation.

The molecular pathway by which the normal squamous mucosa of the distal esophagus is transformed into a columnar mucosa remains uncertain. Tobey et al. [16] showed that acid damage of the esophageal epithelium produces dilated intercellular spaces, which in turn reduces the trans-epithelial resistance and increases trans-epithelial permeability. This change in permeability permits molecules as large as 20 kD to diffuse across the epithelium, exposing stem cells in the basal layer to refluxate. The intercellular acidification exposes the squamous basolateral membrane to acid, initiating a cascade of events leading to loss of cell osmoregulation, cell edema and ultimately cell death [17]. Cell death is counterbalanced by tissue reparative processes, including restitution and replication. It is worth mentioning that during the normal growth process of the embryo, the esophageal cells undergo a columnar to squamous transition under the influence of a combination of active prosquamous and inactivated procolumnar homeobox genes. The cellular phenotype may reverse if the opposite set of cell patterning genes is reactivated. An acidic milieu, combined with other components of refluxate, may induce phenotypic transformation of squamous cells into columnar mucosal cells. The reason why pluripotent esophageal stem cells turn into columnar cells in this "acid environment" may be related to the better adaptability of this epithelium due to its acid resistance. Nevertheless, the origin of BE remains obscure. There are several hypotheses concerning the origin of these stem cells that will give rise to BE [18–20]:

1. Migration and differentiation of stem cells from the gastric cardia.
2. Differentiation of stem cells residing in the crypts of the esophageal mucosal glands.
3. Migration of stem cells from the bone marrow (circulating stem cells that can hone in to areas of injury to repair damaged tissue).

While the transition between squamous and columnar epithelium likely occurs within a few years, the development of intestinal metaplasia may take over 5–10 years [21]. Once the columnar epithelium is established, two possible pathways are observed. The first one, "*gastric differentiation*", implies the formation of parietal cells within glands and may represent a favorable change, as this mucosa is not thought to be premalignant. The second one, "*intestinal differentiation*", induces the expression of intestinalizing genes, causing the formation of goblet cells within the columnar epithelium. The development of intestinal metaplasia is considered a detrimental change because this mucosa is capable of further progression to epithelial dysplasia and adenocarcinoma. The specific cellular event(s) that induce the "intestinalization" of the columnar epithelium is unknown. However, it is likely to occur in response to multiple noxious luminal contents rather than to acid reflux only. In fact, previous studies have demonstrated the association between BE and the exposure of a mixture of acid and bile salts on the esophagus [22–24]. The role of refluxed bile in the development of intestinal metaplasia was suggested by Oberg et al. [25] as patients with intestinal metaplasia had similar esophageal acid exposure to those with GERD and no BE, but significantly higher frequency of abnormal bilirubin exposure. It has been hypothesized that in a weakly acidic environment (pH 3–5), certain bile acids become non-ionized and able to cross the cell membrane. Once inside the cell (pH 7) they become ionized and remain trapped causing mitochondrial injury,

cellular toxicity and mutagenesis [26]. The molecular mechanism by which bile acids promote the development of goblet cells may be related to the activation of the Caudal-related homeobox 2 (Cdx2) promoter via nuclear factor kappa B (NF-κB) with the consequent production of Cdx2 protein in esophageal immature keratinocytes, resulting in the production of MUC2 (intestinal-type protein found in Barrett's metaplasia) [27]. Recently, bile acids have shown to enhance cytoplasmic expression of the signaling ligand Delta-like 1 (Dll1) which facilitates the intestinal metaplasia in conjunction with Cdx2 expression [28].

Pathophysiology: From Barrett's Esophagus to Esophageal Adenocarcinoma

BE is a premalignant mucosa with increased proliferation rates and decreased apoptosis rates compared to normal epithelium [29]. In fact, it is the only known precursor of esophageal adenocarcinoma. However, only a small percentage of patients with BE will develop cancer, and more than 90% of the patients with the diagnosis of esophageal adenocarcinoma have no prior history of BE [30, 31]. The question as to why some cases of BE progress to esophageal adenocarcinoma and some do not remains unanswered. Currently, the presence and grading of dysplasia is the most important predictive factor for the development of adenocarcinoma. The known risk factors for the development of dysplasia in BE include: increasing length of BE, advancing age, central obesity, tobacco usage, lack of non-steroidal anti-inflammatory agent use, lack of proton-pump inhibitors (PPI) use and lack of statin use [10].

Gopal et al. [32] showed that the prevalence of dysplasia was strongly associated with age and length of BE. Patients with BE without dysplasia were younger than those with dysplasia (62 ± 0.8 years vs. 67 ± 1.7 years, $p = 0.02$), and the risk of dysplasia increased by 3.3%/year of age. Patients with BE length ≥3 cm also had a significantly greater prevalence of dysplasia compared to length < 3 cm (23% vs. 9%, $p = 0.0001$), and the risk of dysplasia increased by 14%/cm of increased length. Hampel et al. [33] reported that obesity was associated with a statistically significant increase in the risk for GERD complications and esophageal adenocarcinoma. Interestingly, Singh et al. [34] found that, compared with patients with normal body habitus, patients with central adiposity had a higher risk of BE, even after adjusting for body mass index and presence of GERD, suggesting a reflux-independent association between truncal obesity and BE. Added to this, central adiposity was associated with higher risk of adenocarcinoma (OR 2.5, 95% CI 1.54–4.06) compared with normal body habitus. The relationship between BE and cigarette smoking was reported by Andrici et al. [35] who found that having ever smoked was associated with an increased risk of BE compared with non-GERD controls but not when compared with patients with chronic GERD, suggesting that the increased risk of BE associated with tobacco usage may be due to the increased incidence of GERD in cigarette smokers.

Some medications have been shown to reduce the risk of progression to dysplasia or esophageal cancer in patients with BE. A recent meta-analysis showed that PPI use was associated with a substantial reduction in risk of high-grade dysplasia and/or esophageal adenocarcinoma in patients with BE (OR 0.29 95% CI 0.12–0.79) [36]. There was also a trend towards a dose-response relationship with PPI use for >2–3 years. Another meta-analysis reported that aspirin use also reduced the risk of high-grade dysplasia/adenocarcinoma, as well as non-aspirin cyclooxygenase inhibitors in patients with BE [37]. The chemopreventive effect seemed to be independent of duration of therapy. Finally, statin usage was also associated with a significant (41%) decrease in the risk of esophageal adenocarcinoma within patients with BE [38].

There are four categories to stratify the dysplastic process: (1) no dysplasia; (2) indefinite for dysplasia; (3) low-grade dysplasia; (4) high-grade dysplasia. The development of EAC is characterized by the progression from BE metaplasia to

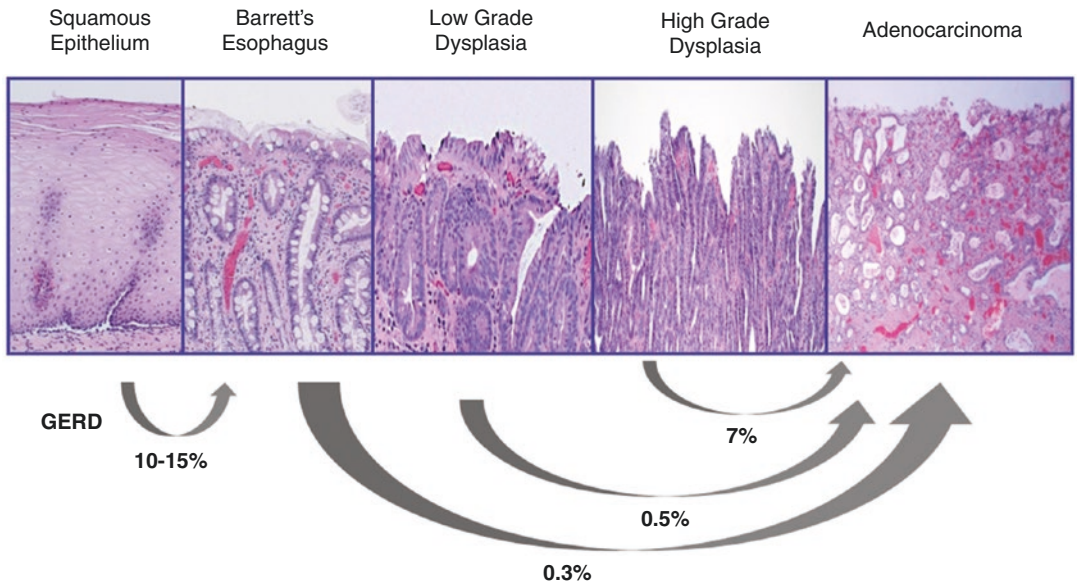

Fig. 3.3 Pathological progression from normal esophageal squamous epithelium to adenocarcinoma (pooled annual incidence)

dysplasia, and ultimately invasive adenocarcinoma (Fig. 3.3). Patients with non-dysplastic BE have very low risk for malignant progression and a recent meta-analysis reported that the pooled annual incidence of adenocarcinoma in this cohort was 0.33% (95% CI 0.28–0.38) [39]. For patients with low-grade dysplasia, Singh et al. [40] reported a pooled annual incidence of 0.5% for adenocarcinoma (95% CI 0.3–0.8). Patients with high-grade dysplasia present an annual incidence of adenocarcinoma of 7% (95% CI 5–8) [41].

Conclusions

The increase incidence of EAC has been attributed to the rising prevalence of obesity and GERD. The latter, is considered the strongest risk factor for EAC, together with its more severe manifestation, Barrett's esophagus. This metaplastic lesion due to the chronic injury produced by repeated reflux episodes involves genetic mutations that can lead to a malignant transformation. Therefore, the pathophysiology of EAC can be depicted by the progression from Barrett's esophagus metaplasia to dysplasia, and ultimately invasive adenocarcinoma.

Conflict of Interest Francisco Schlottmann, MD MPH and Marco G. Patti, MD declare that they have no conflict of interest.

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Staging of Esophageal Cancer: Implications for Therapy

4

Jonathan Cools-Lartigue, Daniela Molena, and Hans Gerdes

Introduction

Contemporary management of esophageal cancer is stage specific and highly complex. Available treatment options have evolved over the past several years and include endoscopic organ sparing techniques, minimally invasive esophagectomy, and multimodality therapy comprising surgery in conjunction with systemic chemotherapy with or without radiation [1, 2]. The organ preserving modalities, including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have been applied with excellent results in node negative disease with tumors confined to the most superficial layers of the esophageal wall (T1a) [3]. In appropriately selected patients, survival rates in excess of 80–90% at 5 years have been observed with considerably less morbidity than esophagectomy [3]. Surgery alone, namely esophagectomy and lymph node dissection, is currently preferred for patients with more advanced local disease (T1b-T2) in the absence of clinical suspicion of nodal involvement [4]. This being said, esophagectomy remains the mainstay of curative intent therapy in patients with esophageal cancer [4]. Patients with more advanced tumors (T3), or those who harbor node positive disease (N+) are at prohibitive risk for systemic spread when treated with surgery alone [1, 2, 5, 6]. Accordingly, multimodality therapy is employed in this context with improved overall, and disease free survival as is demonstrated by contemporary randomized studies [1, 2, 5, 6].

Given the reported outcomes associated with available treatment modalities, appropriate selection is predicated on accurate staging [7, 8]. Accordingly, several staging modalities have emerged and, like the treatment of esophageal cancer, their appropriate implementation is nuanced and complex. Current modalities include imaging via computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), endoscopic ultrasound (EUS), and histopathologic based staging including EMR, ESD, and minimally invasive surgical staging. In the current chapter, the application, strengths, and weaknesses of the various staging modalities will be discussed. It is important to note that no specific modality is sufficient to accurately stage every patient presenting with esophageal cancer by itself. Instead, the various modalities

J. Cools-Lartigue · D. Molena (✉)
Department of Surgery, Thoracic Surgery Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA
e-mail: jonathan.cools-lartigue@mail.mcgill.ca; molenad@mskcc.org

H. Gerdes
Department of Gastroenterology, Hepatology, and Nutrition, Memorial Sloan Kettering Cancer Center, New York, NY, USA
e-mail: gerdesh@mskcc.org

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should be viewed as complementary to one another. Thus, their appropriate implementation is necessary to achieve accurate staging, which is critical to formulate an optimal therapeutic strategy needed to achieve favorable outcomes in this vulnerable patient population.

Contemporary Esophageal Cancer Staging

Esophageal cancer staging is currently performed according to the 8th edition of the AJCC manual and follows the TNM classification (Table 4.1) [9]. Separate stage groupings are provided for the two major histologic subtypes, namely squamous cell carcinoma (SCC) and adenocarcinoma (ADC). For both ADC and SCC, T0 disease denotes high-grade dysplasia; T1 disease is divided into T1a and b and denotes absence or presence of invasion through the muscularis mucosa into the submucosa, respectively. T2 denotes invasion into the muscularis propria, T3 denotes invasion to the adventitia, and T4 denotes invasion into surrounding structures. This is further subdivided in T4a, defined as resectable disease (including diaphragm, pleura, and pericardium) and T4b, defined as unresectable (including trachea, aorta and, vertebral body) [9].

Nodal disease is classified as N1 if fewer than three nodes are involved, as N2 if 3–6 nodes are involved, and N3 if seven or more are involved. Any extra nodal metastases are classified as M1.

Non-anatomic factors also play a role in prognosis, including histologic subtype and tumor grade. Squamous cell carcinoma carries a poorer stage specific prognosis compared to ADC in general. Furthermore, well and moderately differentiated tumors (G1-2) are associated with improved survival in both SCC and ADC compared to poorly differentiated tumors, as reflected by the stage grouping. Finally, prognosis in SCC is affected by tumor location, with upper and middle third tumors carrying a poorer prognosis compared to tumors of the distal third of the esophagus [9].

Early stage disease is defined as T1b or less with no nodal involvement and no sites of metastasis. Patients with true T0-T1a disease can be managed with organ preserving modalities including EMR and ESD. Patients with T1b disease are typically managed with esophagectomy and lymph node dissection, with organ preservation reserved for highly selected cases with good prognosis features on histopathologic assessment, and in whom the presence of medical

Table 4.1 AJCC 8th edition staging of esophageal cancer

	Clinical criteria
T stage	
Tx	Cannot be assessed
T0	High-grade dysplasia—confined by basement membrane
T1a	Invades lamina propria or muscularis mucosa
T1b	Invades into submucosa
T2	Invades muscularis propria
T3	Invades adventitia
T4a	Invades pleura, pericardium, azygos vein, diaphragm, peritoneum
T4b	Invades adjacent structures such as aorta and vertebral body
N stage	
NX	Cannot be assessed
N0	0 involved nodes
N1	1–2 involved regional nodes
N2	3–6 involved regional nodes
N3	7 or more involved regional nodes
M stage	
MX	Cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
ADC grade	
GX	Cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
SCC grade	
GX	Cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
SCC location	
LX	Cannot be assessed
Upper	Cervical esophagus to azygos vein
Middle	Lower border of azygos vein to inferior pulmonary vein
Lower	Inferior pulmonary vein to stomach

Table 4.1 (continued)

	Clinical criteria		
Clinical (c) stage	**T**	**N**	**M**
ADC			
0	Tis	N0	M0
I	T1	N0	M0
IIA	T1	N1	M0
IIB	T2	N0	M0
III	T2	N1	M0
	T3-4a	N0-1	M0
IVA	T1-4a	N2	M0
	T4b	N0-2	M0
	T1-4	N3	M0
IVB	T1-4	N0-3	M1
SCC			
0	Tis	N0	M0
I	T1	N0-1	M0
II	T2	N0-1	M0
	T3	N0	M0
III	T3	N1	M0
	T1-3	N2	M0
IVA	T4	N0-2	M0
	T1-4	N3	M0
IVB	T1-4	N0-3	M1

ADC adenocarcinoma, *SCC* squamous cell carcinoma

comorbidities significantly increases the risk of surgical management. T2 disease can be treated with esophagectomy and lymph node dissection alone with the omission of systemic therapy [4]. Conversely, patients presenting with locally advanced disease, defined as T3 or N positive require a multimodal therapeutic approach [1, 2, 5, 6]. Deciding on the appropriate therapy and subjecting patients to their respective risks is therefore dependent on the determination of clinical stage. In keeping with the expanded spectrum of available treatment modalities, the techniques available for accurate staging are similarly broad and include both imaging and invasive studies. The former group includes endoscopic ultrasound (EUS), CT and PET scan. More invasive modalities include EMR and ESD, as well as minimally invasive staging using diagnostic laparoscopy [8]. These modalities all have their associated strengths and weaknesses and should be viewed as complementary tools in the assessment of disease spread in patients with newly diagnosed esophageal cancer.

Staging Modalities

CT

CT scan is the most commonly employed staging modality at the time of diagnosis of esophageal cancer. It provides a wealth of information regarding all stages of disease from the primary tumor itself (T stage), to nodal (N stage), and distant metastasis (M stage). Furthermore, as the majority of patients with esophageal carcinoma present with advanced disease, CT can be employed early on, obviating the need for instrumentation of a narrowed esophageal lumen, which is a common feature of locally advanced tumors [7]. It is important to note however, that the performance characteristics of CT are different with regards to T, N and M stage. Overall, CT is excellent at identifying T4 lesions and sites of metastatic foci. Conversely, imaging findings are progressively more subtle, and thus less accurate in earlier stages of disease [7].

CT and T Stage

Multidetector CT scanners are able to provide volumetric data on the primary tumor and have demonstrated an overall accuracy of 80% in the determination of T stage. Stage specific accuracy using multi detector CT ranges between 75% and 84.5% [7, 10]. This being said, CT performs relatively poorly with respect to accurate T stage identification in early stages, as depth of invasion through the actual layers of the esophageal wall cannot be directly assessed. Thus, differentiation of T1 from T2 tumors with CT is difficult. For example, a recent meta-analysis comparing the accuracy of CT with respect to T-stage as compared to final histology demonstrated an accuracy of 63% for T1 lesions compared to 75.3% for T3 lesions [7, 10]. Accuracy in identifying more advanced disease can be obtained via the addition of oral contrast. In this manner, luminal obstruction can be demonstrated, and these tumors carry a high risk for invasion into the muscularis propria and adventitia (T3) [7]. Furthermore, invasion through the esophageal wall and into adjacent structures (T4) can be

determined with a high degree of accuracy. In particular, gross invasion into the tracheobronchial tree, aorta and heart can be specifically assessed. Tumor contact of 90° or more with the aorta or loss of the fat space between the aorta, esophagus and spine portend invasion. Loss of the fat plane between the esophagus and airway, direct contact or bulging against the adjacent membranous airway and visualization of a tracheoesophageal fistula are similarly ominous features. Finally, pushing of the tumor against the pericardium with associated indentation or pericardial effusion are concerning for invasion. Accordingly, the sensitivity of CT scan for the detection/exclusion of T4 disease has been estimated at 100% in some series with the specificity varying widely between 52% and 97% [7, 10–12].

Tumor location also affects the accuracy of CT scanning in determining T stage [7, 13]. For example, in the study by Parry et al., 266 patients with histologically proven GEJ carcinoma were assessed. There final pathologic stage was compared to their clinical stage including data obtained by CT. The authors demonstrated that in GEJ tumors, the overall accuracy of CT was 61%, significantly lower than what was observed for endoscopy/EUS (91%). For patients harboring Siewert I, II, and, III tumors, accuracy of CT was 69%, 57%, and 80% respectively [13].

CT and N Stage

CT has also demonstrated some utility in identifying nodal metastasis. Supraclavicular nodes >5 mm and intrathoracic nodes >10 mm in short axis are considered metastatic. Retrocrural nodes >6 mm and left gastric nodes >8 mm in short axis are considered suspicious. Lymph nodes with heterogeneous or increased enhancement as well as clusters of three or more LN are similarly considered suspicious [7]. However, CT scanners provide limited accuracy with regards to nodal staging. Given the non-invasive nature of the study, tissue acquisition and histologic confirmation is not possible. Furthermore, CT scan is likely to understate small nodal disease given its ability only to detect enlarged lymph nodes [7]. This has the added effect of overestimating the importance of reactive lymph nodes. In addition, metastatic lymph nodes may be missed when they are difficult to visualize as separate from the primary tumor. Along these lines, CT scan demonstrates an overall accuracy of at best 66% in nodal staging. The study by Luketich et al. demonstrated a sensitivity and specificity of 33% and 88% respectively in the identification of node positive disease within the chest and abdomen, proving to be inaccurate in more than 40% of patients [8, 14].

CT and M Stage

With respect to metastatic disease, CT scan is the imaging modality of choice for the detection of pulmonary and liver metastases. Sensitivity with respect to the detection of bony metastases is reduced compared to PET and radio nucleotide scanning however. Furthermore, CT demonstrates relatively poor accuracy in the identification of peritoneal disease [7, 14, 15]. Overall, CT is able to correctly identify metastatic disease 82% of the time [7]. For a summary of the performance characteristics of CT in the staging of esophageal cancer, see Table 4.2.

Collectively, the data supports the use of CT as an excellent initial test in guiding further staging efforts. Patients with seemingly early stage disease may be candidates for organ preserving endoscopic therapies and such observations would mandate staging modalities suited to more precisely define T stage such as EUS, ESD or EMR [3, 7, 16, 17]. Conversely, patients with overt luminal obstruction or invasion into surrounding structures could forego such interventions and proceed to modalities more apt to define resectability and the appropriate implementation of multimodality curative intent therapies [7]. This centers more on accurate determination of M stage with complementary staging modalities such as PET CT and diagnostic laparoscopy [7, 8, 18].

Table 4.2 Performance characteristics of CT, MRI, CT-PET and EUS in the diagnostic workup of esophageal cancer

Modality	Sensitivity	Specificity	Accuracy
CT			
T1, 2, 3, 4	–	–	63%, 72.9%, 75.3%, 74.9% [7]
N	77.2%	78.3%	66.1–87% [7]
M	–	–	81% [7]
M peritoneum	58.8%	98.6% [33]	
M peritoneum	66% [32]		
MRI			
T	–	–	81% [20]
T4b	86–100%	67–84%	75–87% [21]
N	25–62%	67–88% [21]	
M	–	–	–
CT-PET			
T1/2	26–63% [7] 43% [25]	–	–
T3/4	83–100% [7]	–	–
N	24–99%	46–98% [7]	
M	69–78%	–	82–88% [7]
EUS			
T	27.9%	90.9%	79.4% [17]
			66–97% GEJ
T1	81.6%	99.4%	
T2	81.4%	96.3%	
T3	91.4%	94.4%	
T4	92.4%	97.4% [28]	
T0/2vsT/34	79%	94%	85% [26]
N	73%	77% [26]	
	35.3%	90.9%	57.1% [16]
w/o FNA	84.7%	84.6%	
w FNA	96.7%	95.5%	
N stage in uT1	0%	90%	
uT3	83%	55% [28]	

MRI

MRI and T Stage

Currently, limited evidence supports the use of MRI in the staging of esophageal cancer due predominantly to wide variability in its performance across a number of studies [7]. This reflects a lack of uniform techniques for image acquisition and differences in image quality observed over time related to the specific MRI technology used. For example, with respect to T staging, the study by Sakurada et al. was able to demonstrate that T2 weighted and diffusion gated images were able to correctly identify T1,2 3 and 4 disease in 33%, 58%, 96% and 100% of analyzed cases [19]. Similarly, the results of contemporary studies have demonstrated high degrees of accuracy with respect to the overall performance of MRI in T staging. In particular, T2 weighted MRI with cardiac triggering was able to correctly identify T stage in 81% of patients with an overall rate of over and understating of 16% and 3% respectively [20].

Additional studies have been decidedly less optimistic. For example, the overall accuracy of combined T1 and T2 weighted MRI in the determination of T stage has been estimated at approximately 60% [21]. In particular, MRI appears to be particularly poor at differentiating between <T3 and T3 or greater tumors with a sensitivity and specificity of 40% and 63% respectively [21]. This differentiation represents a critical decision point for selecting patients in need of neoadjuvant therapy and those who do not, thus rendering MRI ineffective to this end [4]. However, MRI does appear to perform well when trying to differentiate resectable T4a from unresectable T4b disease. In this respect it has demonstrated a sensitivity, specificity and accuracy of 86–100%, 67–84%, and 75–87% respectively [21].

MRI and N Stage

With respect to N staging, a great deal of heterogeneity exists amongst contemporary studies outlining the utility of MRI in esophageal cancer patients. Current estimates of sensitivity and specificity vary between 38–70% and 67–93% respectively. This range is attributable to varying techniques of image acquisition and threshold size (10 versus 5 mm) for identification of suspicious lymph nodes [21].

Collectively, the data suggest that MRI represents a promising modality in esophageal cancer

staging. However, standardized image acquisition techniques are lacking and while additional research into the optimal role for MRI in the staging of esophageal cancer is ongoing, it currently demonstrates little benefit over CT at increased cost and decreased availability [10, 19–21]. Thus, it is reasonable that its current use be predicated on institutional experience or equivocal findings with respect to delineating T4a from T4b disease based on available CT data [10, 19–21]. Like CT, equivocal findings can be further evaluated and potentially validated with complementary modalities such as EUS, EMR and ESD for suspected early stage disease and PET and/or surgical staging for more advanced disease [10, 19–21].

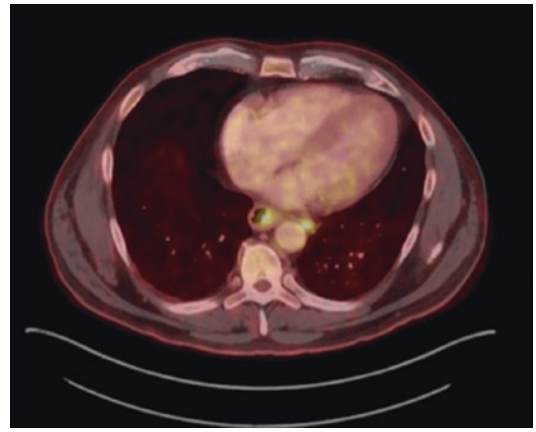

Fig. 4.1 PET CT demonstrating a PET avid distal esophageal lesion and peri-esophageal lymph node

MRI and M Stage

To date limited data assessing the ability of MRI to detect distant metastasis exists. Accordingly, its role in the assessment of metastatic disease remains unclear. For a summary of the performance characteristics of MRI in the staging of esophageal cancer, see Table 4.2.

PET CT

PET-CT has emerged as an important modality in the staging of esophageal cancer [18, 21–23]. PET relies on the expression of the GLUT-1 glucose transporter on neoplastic cells for the uptake of FDG glucose thus providing information regarding the metabolic activity of the tumor in addition to anatomic information [7, 21]. With respect to anatomic localization, PET images can be fused with CT images to more effectively localize sites of increased or abnormal physiologic glucose uptake (Fig. 4.1). Accordingly, contemporary PET imaging consist of fused PET and CT images.

A high proportion of both ADC and SCC tumors are PET avid with approximately 20% of adenocarcinomas showing little or no FDG avidity [24]. This is particularly true in tumors displaying a diffuse growth pattern, often seen in poorly differentiated and signet cell lesions [24]. Squamous cell carcinomas tend to be more PET avid than ADC in general with an average SUV of 13.5 versus 9.1 respectively [7, 10, 21, 24]. Given these features, the rate of primary tumor detection with CT-PET is currently estimated at 92.7% based on the results of recent meta-analysis [21]. With respect to differentiating between T stages, PET-CT cannot differentiate the depth of invasion of the primary tumor and there is a high likelihood that early (Tis, T1) lesions will be missed altogether given the resolution of this modality. Accordingly, stage specific sensitivities for CT-PET have been reported in gastric and GEJ tumors (26–63% T1/2 tumors versus 83–100% for T3/4 tumors). Like CT scanning, PET-CT is able to provide important information on T stage in patients with obstructive lesions in whom endoscopy is not feasible [7, 21, 24]. False positive results can be obtained in patients with active infectious or inflammatory processes such as esophagitis [7, 21, 24].

One of the advantages of PET-CT is in its ability to provide information regarding tumor metabolic activity. This has implications with respect to prognosis, and even in the absence of visualized nodal metastasis, this can predict the incidence of lymphatic involvement [18, 22, 23].

For example, in the study by Risk et al., 488 patients with seemingly operable esophageal cancer were subject to CT-PET and their SUV max was analyzed with respect to pathologic stage and survival. Patients were stratified according to their SUV max into low and high SUV groups with a

threshold of 4.5. Patients in the low SUV group demonstrated earlier T stage tumors and a lower incidence of nodal metastasis. In patients with SUV less than 4.5, 90% were found to harbor T1 or T2 lesions and only 8% were ultimately found to harbor N1 or M1a nodes (according to the AJCC 6th edition). Conversely, in patients with an SUV max >4.5, only 60% were ultimately found to harbor T1 or T2 tumors and 45% were found to be N1 or M1a node positive. Furthermore, this was found to correlate independently with survival, with patients in the low SUV max group demonstrating significant improvements in overall survival independent of stage [22].

The value of CT-PET in the workup of patients with esophageal cancer in the pre and post neoadjuvant setting has been demonstrated in prospective studies. The ACOSOG Z0060 prospectively evaluated 189 patients with surgically resectable esophageal carcinoma following standard staging at the time including mandatory CT scan of the chest and abdomen and bone scan, CT or MRI of the brain as clinically indicated. Patients who were identified as T1-3, N0-1 and M0-1a (according to the 6th edition staging manual) were eligible for study enrolment which added PET alone to the staging work up. The aim of the study was to determine the usefulness of the addition of PET (without CT at the time of the study) to standard complete staging. The authors were able to demonstrate an increase in the detection of metastases precluding surgical resection in 4.8 ± 9.5% of patients. Furthermore, PET identified N1 disease in 45/189 (23%) patients staged N0 by CT. This lead the authors to conclude that at least a subset of patients were subject to induction therapy who otherwise would not have been without the addition of PET [18]. Contemporary studies employing PET-CT have mirrored the results laid out in the ACOSOG Z0060 study. Current estimates regarding the ability of PET to alter the surgical management of patients with esophageal cancer hover in the range of 20–40%, predominantly due to the ability of PET-CT to identify occult metastatic disease [7, 10, 21, 24]. For a summary of the performance characteristics of PET-CT in the staging of esophageal cancer, see Table 4.2.

Overall, the data demonstrate that PET-CT provides a great deal of information in identifying patients at high risk of nodal and distant metastatic spread based on the metabolic activity of the primary tumor itself. In addition, it is able to identify occult metastatic disease leading to tangible changes in patient management in as many as 40% of patients [25]. These features must be interpreted carefully with respect to a given patients clinical presentation. For example, given the relatively low resolution, and thus detection threshold of the study, PET CT is of limited value in early T1 disease. Furthermore, ADC, particularly poorly differentiated and signet ring lesions are more likely to demonstrate low or no PET avidity compared to well differentiated lesions, potentially limiting the use of PET-CT in these patients [7, 10, 21, 24].

EUS

Endoscopic ultrasound has emerged as the preferred first line modality for the assessment of loco regional disease in esophageal cancer [7, 13, 17, 26]. This modality allows the identification of subtle mucosal changes, accurate anatomic localization and the potential to acquire tissue for histologic analysis and subsequent diagnosis. Echoendoscopes with probes of 7.5–12 MHz demonstrate five layers of the esophageal wall according to echogenicity. These are as follows: (1) superficial mucosa (2) deep mucosa (3) submucosa (4) muscularis propria, (5) adventitia [7, 8, 13] (Fig. 4.2).

EUS and T Stage

The role of EUS in staging loco regional disease in patients with esophageal cancer has been extensively studied and to date, the bulk of data with regard to sensitivity and specificity arise in the setting of 7.5–12 MHz probes [7, 8, 13]. In general, this technique demonstrates an overall sensitivity and specificity of 85–90% and an accuracy of 70–80% in the assessment of T stage. However, this modality is not without its limitations. EUS is quite poor at discerning T stage in early lesions. EUS has been reported to accurately

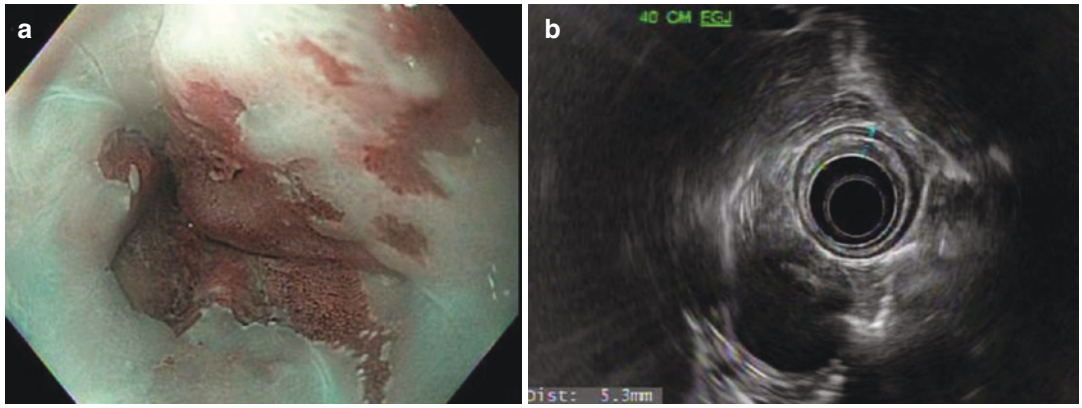

Fig. 4.2 Endoscopic evaluation of suspected early esophageal cancer. (**a**) Narrow band imaging demonstrates a mucosal irregularity with a small nodule in the background of Barrett's esophagus at the level of the esophagogastric junction. (**b**) EUS shows a thickened mucosa without clear nodules or masses

stage only 39% of T1a lesions and approximately 50–70% of T1b lesions. A previous study also showed that the accuracy drops when tumors are identified to be T2 or greater on CT [27]. Higher resolution probes seem to improve the accuracy of T staging in early lesions to 64% [7, 16].

This data has been consistent across studies. In the meta-analysis by Puli et al., the sensitivity and specificity of EUS in the determination of T stage was determined based on the aggregate results of 49 studies [28]. For T1, T2, T3 and T4 disease the sensitivity and specificity are 81.6%, 99.4%, 81.4% and 96.3%, and 91.4%, 94.4%, 92.4% and 97.4%, respectively. As previously staged, EUS performs better in more advanced T3-4 tumors than earlier stage T1-2 tumors with an accuracy of >90% versus 65% according to the same study [28].

EUS and N Stage

Endoscopic ultrasound in addition to providing information on T stage, can visualize enlarged periesophageal nodes as well as obtain tissue for histopathologic diagnosis via EUS guided fine needle aspiration (FNA) [28]. Characteristics of lymph nodes that portend malignant involvement include *size greater than 10 mm in long axis*, a *hypoechoic appearance*, *round shape* or *sharp distinct margins* [7, 8, 13, 14, 17, 28]. EUS demonstrates a sensitivity and specificity that ranges between 59.5–100% and 40–100% respectively. More precise estimates have reported the sensitivity, specificity and accuracy of EUS at 85–97%, 85–96% and 75% respectively for differentiating LN positive disease from LN negative disease [7, 8, 13, 14, 17, 28]. Overall, the false negative rate for EUS is 18% and the false positive rate is 9% [7, 8, 13, 14, 17, 28].

This range in performance of EUS observed may be partly attributable to the fact that fewer than 25% of metastatic lymph nodes demonstrate all four of the suspicious features listed above. Furthermore, the accuracy of EUS is affected by lymph node station [7, 8, 13, 14, 17, 28]. In general, EUS demonstrates the best performance in identifying positive aorto-pulmonary window and paratracheal nodes (accuracy 91 and 89% respectively) [7, 8, 13, 14, 17, 28]. Accuracy for the identification of subcarinal, paraesophageal, and pericardial nodes are similar ranging from 75% to 79%. Accuracy is poorest in the identification of lesser curvature lymph nodes, with a reported accuracy of 51%. When combined with fine needle aspiration biopsy (FNAB), the false positive rate is <1% [7, 8, 13, 14, 17, 28].

In addition to location, the size of the metastatic focus can significantly impact the performance of EUS. For example, in the study by Foley et al., the authors analyzed the performance of EUS alone in a contemporary cohort of patients with esophageal and esophago-gastric cancer. Patients had mixed histology (89% adenocarcinoma, 10%

SCC, 1% neuroendocrine). The sensitivity and specificity of EUS in the cohort was 42.6% and 75% respectively. Overall, EUS correctly distinguished N0 from N+ disease in 55.4% of patients. Furthermore, EUS was found to be significantly more likely to under stage as opposed to over stage patients with node positive disease. In patients incorrectly staged as N0, the pathologic features of involved lymph nodes were assessed. Overall, the median size of involved lymph nodes was 6 mm, with a tumor focus of 3 mm. However, 82% of missed LN were <6 mm in size. Furthermore, 44% of missed LN metastases were found in LN <2 mm in size (micro metastasis). Identification of such small nodes is challenging and often precludes further analysis by FNAB [16]. Taken together, the data suggests that overall; EUS alone will miss N+ disease in nearly 50% of patients, with micro metastatic disease. Thus, understaging of patients with LN+ disease continues to be a limitation of EUS as an imaging modality. However, the identification of positive LN is likely to be accurate [16].

The data suggesting that small foci of metastasis in N+ patients continue to be missed by EUS is consistent over time as demonstrated in the study by Cen et al. [3]. Therein, the sensitivity, specificity and accuracy of EUS in the identification of node positive patients who were naive to any preoperative therapy was assessed. Of the 87 patients included in the study, the overall N+ rate was 21/87 (24%) [3]. The sensitivity specificity and accuracy of EUS were 38%, 94% and 81% respectively. Again, patients were more likely to be understaged (15%) than overstaged (4.6%) [3]. For a summary of the performance characteristics of EUS in the staging of esophageal cancer, see Table 4.2.

Clinical Impact of EUS

Given the excellent performance characteristics listed above, the tendency is to overestimate the efficacy of EUS in the staging of patients with esophageal cancer. In fact, limitations do exist. First, EUS is highly operator dependent. Second, in patients with luminal obstruction due to tumor, EUS may limited as the endosonoscope is unable to pass the tumor and the staging is limited to the top of the tumor and the mediastinum above the level of obstruction only. Finally, there is a risk of both over- an under-staging the T and N stage when employing EUS. With respect to the latter, the magnitude of this problem is unclear as patients who demonstrate T3 or greater disease are already candidates for multimodal therapy, obviating the need to necessarily identify node positive disease in this context. Conversely, the importance of identifying node positive disease is extremely important in seemingly early stage disease. Along these lines, a number of studies have sought to characterize the real-world performance of EUS in the management of patients with esophageal carcinoma [26, 29]. The study by Harewood et al. examined the utility of EUS from the standpoint of oncologic outcome in patients with esophageal cancer [29]. A total of 60 patients staged via CT alone prior to the implementation of routine staging EUS were compared to 107 patients evaluated with CT and EUS (after the introduction of routine staging EUS). The authors demonstrated a significant increase in the utilization of neoadjuvant therapy in patients who underwent EUS staging compared to those that did not (32.7% versus 15%). This was attributed to improved identification of locally advanced disease (T2-T3 N1) as the result of the addition of EUS to CT compared to patients subject to CT alone. This was associated with improved overall survival at median follow up of 22 months in EUS staged patients (58.9%) versus CT alone (47.7%). When adjusting for tumor size, location, and stage the hazard ratio for death was 0.66 in favor of EUS (95% CI 0.47–0.9 $p = 0.008$). Thus, by improving preoperative stage determination, patients may be more likely to receive treatment associated with improved survival, confirming the utility of EUS in the preoperative workup of esophageal cancer patients [29].

In keeping with the data presented thus far, it can be surmised that much of the value in EUS lies in its ability to identify patients who require multimodal therapy. Additional studies have confirmed this hypothesis and demonstrated the

ability of EUS to predict outcome. For example, in the study by Barbour et al., 209 patients who underwent preoperative staging with EUS followed by surgery without neoadjuvant therapy were assessed with respect to staging accuracy as determined by histopathologic analysis, and clinical outcome [26]. The authors demonstrated that EUS correctly identified T stage in 61% of patients and N stage in 75% of patients. More importantly, the authors were to stratify patients according to early and advanced stage groups defined as T0-2 N0 and T3/4 N1 respectively based on EUS findings. Patients in the early stage group exhibited higher rates of complete resection (R0) compared to advanced stage patients (100% versus 82% respectively $p < 0.001$). In addition, EUS grouping was highly predictive of disease specific survival with 5-year survival in the early stage group at 65% versus 34% in advanced stage patients. Taken together, this date demonstrates that EUS is highly predictive of patient outcome and can be used to accurately identify patients in need of multimodal therapy. Thus, it demonstrates that this efficacy offers a tangible clinical benefit [26].

A critical element in staging patients with early esophageal cancer is the identification of patients with local only disease. This determination hinges on an accurate assessment of the risk of lymph node metastasis, which itself is dependent in part on T stage. Patients with esophagus only disease are candidates for organ-sparing endoscopic therapies such as EMR and ESD, which are currently recommended in patients with T1a disease or less [3]. Accordingly, the ability of EUS to identify patients with T1a disease alone has been estimated. In the study by Bartel et al., 335 patients with BE (including nodular BE) or early esophageal cancer were assessed using EUS [17]. The sensitivity, specificity, PPV, NPV and accuracy were estimated at 50%, 93%, 40%, 95%, and 90% respectively. Overstaging occurred in 7% of patients and understating in 11%. Collectively, therefore, current data supports the use of EUS in the determination of T stage in patients with esophageal malignancies but clearly demonstrates that it is not without its shortcomings. These can be overcome in part when combined with the resectional techniques encompassed by EMR and ESD [17].

EMR/ESD

The endoscopic resection techniques, including EMR and ESD have demonstrated utility in both staging seemingly early esophageal tumors and in curing them. With respect to the former, submucosal injection that results in raising of the target lesion above the muscularis effectively differentiates T1 from T2 lesions [3]. The latter invade into the muscularis propria, precluding formation of a wheal and endoscopic excision. This can subsequently be confirmed based on the findings at pathologic analysis following excision. This serves both to determine the completeness of resection based on negative margin status and the risk of spread base on a number of other factors including size, depth of invasion, tumor differentiation and lymphovascular invasion (LVI) [3, 30].

From the standpoint of curative resection, EMR is typically reserved for lesions 2 cm or smaller within the esophagus (Fig. 4.3). In larger lesions, ESD is associated with higher rates of curative excision by providing higher rates of en bloc and thus R0 resection [30, 31]. Curative resection in this context is predicated on the absence of nodal metastasis. Along these lines, both modalities have the added advantage of providing tissue for pathologic assessment and thus accurate prediction of the likelihood of occult lymph node metastasis [30, 31]. In the study by Lee et al., the incidence of lymph node metastasis in patients with T1 lesions of the esophagus was determined following esophagectomy and correlated with pathologic features of the primary tumor in order to determine risk factors for occult lymph node positive disease in seemingly early stage patients. These features included tumor size, depth of invasion (T1a versus T1b) degree of differentiation (well, moderate or poor) and the presence of LVI. N1 disease was observed in 7% of patients with T1a disease and 29% of patients with T1b disease. Furthermore, tumor size and the presence of LVI were the strongest

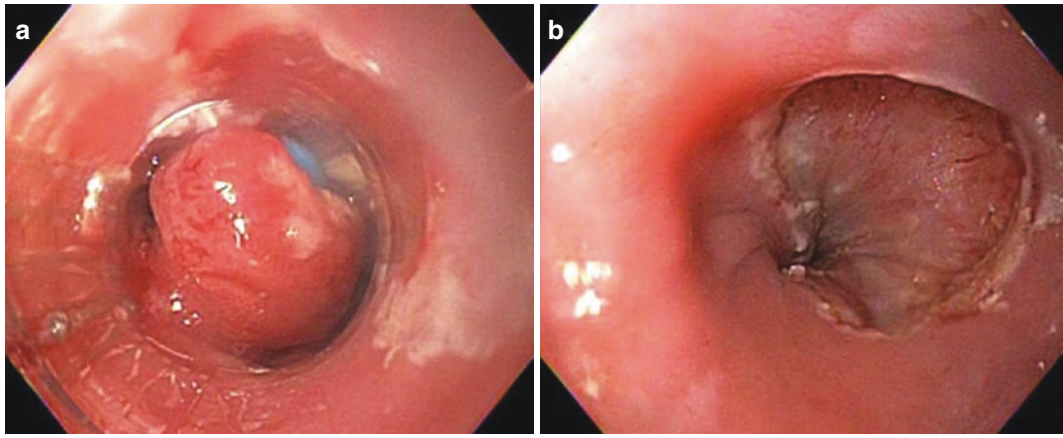

Fig. 4.3 Endoscopic mucosal resection of an early esophageal cancer identified in the background of Barrett's esophagus. (**a**) The mucosal abnormality is sucked within a specialized cap placed at the end of a standard gastroscope. (**b**) The resulting defect demonstrates a resected mucosa, revealing a layer of submucosa and muscularis. Pathology report showed a T1a adenocarcinoma, well differentiated, and without lymphovascular invasion

independent predictors for lymph node positivity. In this study, the authors were able to develop a simple scoring system to quantify the risk of lymph node metastasis (LNM) with patients starting as low (0–1 points), moderate (2–4 points) and high risk (five or more points). Patients in the low risk group have a 2% or less risk of LNM, while patients in the moderate or high-risk groups demonstrate a risk of 3–6% and more than 7% respectively. With this in mind, organ sparing endoscopic techniques such as EMR or ESD are recommended in patients with T1a tumors 2 cm or less that are well or moderately differentiated and LVI negative [30].

Staging Laparoscopy

The role of staging laparoscopy (SL) for the identification of peritoneal disease is well established in patients with esophageal cancer [15, 32–34]. It is recommended for patients with locally advanced GE junction, particularly Siewert III tumors. Its use is associated with a significant reduction in negative laparotomy rate by 23% [15, 32–34]. Furthermore, patients identified to have unresectable disease due to peritoneal involvement identified at SL are more likely to receive palliative therapy compared to patients discovered to be unresectable at the time of planned curative intent surgery [15, 32–34]. Given the dismal prognosis in this patient cohort, optimizing quality of life and minimizing morbidity are paramount and highlight the importance of SL.

Compared to CT, SL has demonstrated superior sensitivity in the diagnosis of peritoneal disease in contemporary studies [15, 32–34]. In the paper by Leeman et al., 74 patients with seemingly resectable EGJ tumors were subject to SL which included both visual inspection of the peritoneal cavity and lesser sac as well as cytologic analysis of peritoneal washings (200cc infused normal saline solution) or ascitic fluid. All patients similarly underwent CT of the chest and upper abdomen with IV contrast according to standard institutional protocols. The authors calculated the sensitivity, specificity, NPV and PPV for SL and CT as 94.1%, 100%, 100%, and 98% for SL versus 58.8%, 89.6%, 66.7%, and 86% for CT, respectively. Furthermore, the authors were able to conclude that in their cohort of patients, 26 of 73 patients (35.6%) were spared unnecessary laparotomy directly as a result of the findings on SL and all were referred for palliative chemotherapy [33].

Similar findings were put forward by Nguyen et al. Over a 3-year period between 1998 and

2001, 33 patients with esophageal cancer were staged using CT scan. Of those 33, 27 also underwent additional staging with EUS. Minimally invasive staging was performed in 24 patients and consisted of diagnostic laparoscopy, fiber optic bronchoscopy, esophagogastroduodenoscopy, and laparoscopic ultrasound of the liver. Imaging via CT revealed resectable disease in 31 of 33 patients. EUS was feasible in 24 of 27 patients and was not feasible in the remaining three due to luminal obstruction by tumor. All patients that underwent complete EUS were thought to have resectable disease. However, at the time of MIS staging, unresectable disease was identified in eight patients due to metastasis. Laparoscopic ultrasonography did not alter management in any patients. Instead, metastatic disease was identified predominantly via diagnostic laparoscopy in six patients or via bronchoscopy in two patients with middle third lesions in whom EUS could not be performed due to luminal obstruction as a result of tracheal invasion. Thus, staging laparoscopy in distal tumors and bronchoscopy in more proximal tumors altered management in 36% of patients studied, precluding non-curative surgery [15].

Even combined imaging modalities are insufficient to reliably identify unresectable disease in locally advanced cases of esophageal cancer. Overall, with respect to abdominal metastasis, conventional imaging via combined CT scan and EUS demonstrate a sensitivity, specificity and negative predictive value of 61%, 91% and 65% respectively. In contrast, SL demonstrated a far superior sensitivity, specificity and negative predictive value of 97%, 100% and 96% respectively [32].

These findings hold true even in contemporary studies employing modern imaging techniques. For example, in the study by de Graaf et al., the authors demonstrated that SL changed surgical management in 20.4% of patients. Overall, 581 patients with esophageal and gastric cancers were staged using CT and EUS. If they were determined to be resectable according to those staging modalities, they were subject to SL. A total of 416 patients ultimately underwent SL. Based on the results of CT alone, the authors calculated a sensitivity of 66% and efficacy of 67% with respect to the detection of peritoneal or hepatic metastases. When combined with EUS, the sensitivity and efficacy were 81% and 65% respectively. These results were determined at the time of curative intent surgery or SL. In the 416 patients who underwent SL, 332 (79.8%) were found to have resectable disease (no intraabdominal metastases) and proceeded to curative intent surgery. Eighty-four patients (20.2%) were discovered to have inoperable disease and thus spared from a laparotomy. The pattern of metastases in the unresectable patients were peritoneal and/or liver metastases (75%), unresectable disease due to invasion of unresectable structures (20.2%), or bulky adenopathy precluding complete resection (4.8%). Overall the sensitivity and specificity of SL were 88% and 100% respectively. In particular, SL was most effective in identifying abdominal metastases in patients with esophageal adenocarcinoma, particularly of the distal esophagus and GEJ. Conversely, no patients with proximal or mid esophageal cancers demonstrated a change in management due to SL. Similarly, only one patient with SCC was found to have abdominal metastases precluding curative resection as determined by SL.

Overall, these results demonstrate that even when combined with EUS, current imaging modalities are not sufficiently sensitive nor accurate to identify patients with unresectable esophageal adenocarcinoma due to abdominal metastases and highlight the importance of invasive staging in patients with locally advanced distal esophageal and EGJ adenocarcinoma [32]. For a summary of the performance characteristics of diagnostic laparoscopic in the staging of esophageal cancer, see Table 4.3.

Table 4.3 Performance characteristics of staging laparoscopy in the diagnostic workup of esophageal cancer

Study	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
Leeman et al.	94.1	100	100	98
Nguyen et al.	97	100	96	–
Graaf et al.	88	100	–	–

NPV negative predictive value, *PPV* positive predictive value

Conclusions

Effective treatment of esophageal cancer is predicated on accurate staging [9, 32, 34]. This has become increasingly important as the therapeutic options in the management of esophageal cancer patients have expanded over time, ranging from organ sparing techniques to esophagectomy in the context of a multimodal regimen [9, 32, 34]. Along these lines, the appropriate treatment regimen is determined by the patients stage of disease [9, 32, 34].

- In patients with T0-T1a disease, EMR or ESD can be employed as curative modalities in patients in whom EUS/FNAB and CT demonstrate an absence of nodal and metastatic disease. Furthermore, in the event of equivocal EUS findings, the resectional modalities can further identify stage and risk factors for nodal involvement based on findings at pathology.
- In patients with true T1b-T2 N0 M0 disease as determined by EUS/FNAB CT and/or MRI and increasingly PET/CT, surgery alone is indicated based on the results of randomized studies [9, 13, 22, 32, 34].
- In patients with >T2 or N positive disease, a multimodality approach is essential to achieve favorable outcomes.

As stage becomes increasingly advanced, particularly in patients with distal esophageal adenocarcinoma, the risk of occult abdominal metastases becomes elevated. As a result staging laparoscopy is essential to ensure that curative intent surgery is possible and to spare palliative patients the morbidity of unnecessary surgery [8, 9, 13, 14, 22, 32, 34].

Blanket application of all the above listed staging modalities remains impractical and represents an inappropriate use of limited resources. The appropriate diagnostic workup hinges in part on patient presentation. In patients who present with a small lesion without dysphagia discovered incidentally or in the context of surveillance for GERD, early disease is likely. In this context EUS and FNAB to determine T and N stage in addition to CT to rule out occult metastasis is sufficient. In patients who present with dysphagia, locally advanced disease becomes more likely. In this context, PET-CT serves as an appropriate starting point. Patients found to be free of occult metastases or node negative should proceed to EUS/FNAB to further characterize the T stage of the lesion, obtain tissue for diagnosis, and clarify the N stage as nodes closely related to the primary lesion are poorly resolved by the imaging techniques alone. Patients found to have bulky abdominal nodal disease, particularly in the context of distal third adenocarcinoma should undergo diagnostic laparoscopy to rule out peritoneal metastasis and further assess resectability (Fig. 4.4).

A meticulous approach to staging is critical to stratify patients according to the treatment modalities that offer them the greatest chance of cure with the lowest pos-

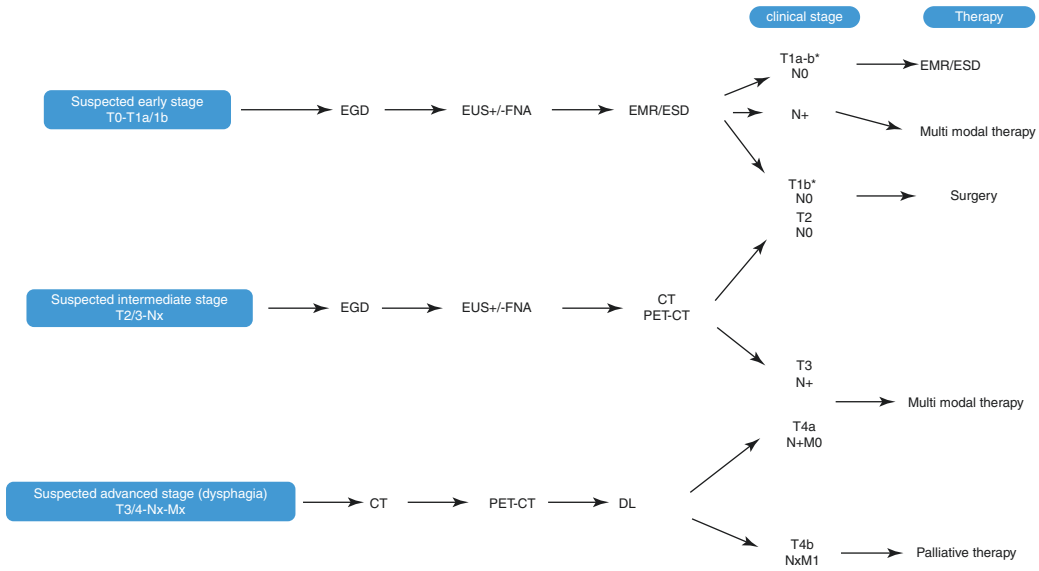

Fig. 4.4 Staging algorithm for patients with esophageal cancer. *EGD* esophagogastroduodenoscopy, *EUS* endoscopic ultrasound, *FNA* fine needle aspiration biopsy, *EMR/ESD* endoscopic mucosal resection/endoscopic submucosal dissection, *DL* diagnostic laparoscopy. T1b* can be managed endoscopically in very highly selected cases

sible morbidity. Each test has it associated strengths, weaknesses and risks and should be applied in a thoughtful manner with the objective of stratifying patients according to risk of local spread to regional lymph nodes and distant sites thus allowing the selection of an appropriate effective treatment strategy.

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Endoscopic Therapy for Superficial Esophageal Cancer

5

Anna M. Lipowska and Irving Waxman

Introduction

Esophageal cancer is the sixth most common cause of cancer mortality worldwide [1]. The majority of esophageal cancers can be classified into two subtypes, adenocarcinoma and squamous cell carcinoma. In recent years, adenocarcinoma has surpassed squamous cell as the more commonly diagnosed esophageal malignancy in the developed world. The two subtypes vary in presentation, risk factors, staging, and approaches to treatment. Endoscopic therapy is a viable treatment alternative to both when the tumor is limited to the mucosal layer of the esophagus.

The esophageal wall is composed of four layers, with the mucosa being the most superficial layer. The mucosa encompasses the epithelium, lamina propria and muscularis mucosa (Fig. 5.1). Immediately beyond is the submucosa, which is made of connective tissue including blood vessels, lymphatics, and Meissner's plexus. The submucosa connects the mucosa to the muscularis propria, made of inner circular and outer longitudinal muscle layers along with the Auerbach plexus. The deepest level comprised of connective tissue is called the adventitia.

A. M. Lipowska · I. Waxman (✉)
University of Chicago, Center for Endoscopic Research and Therapeutics, Chicago, IL, USA
e-mail: Anna.Lipowska@uchospitals.edu; iwaxman@uchicago.edu

Understanding esophageal anatomy and that adenocarcinoma and squamous cell carcinoma are separate entities with different cancer pathogenesis and cancer biology, current guidelines recommend separate staging systems for the two malignancies [2]. Both systems apply the tumor, node, and metastasis (TNM) categories and help guide decision making and therapy. For superficial tumors, carcinoma in situ (Tis) is defined as high-grade dysplasia, or malignant cells confined to the basement membrane. The T1 category can be divided into the T1a subgroup when the tumor invades the laminal propria or muscularis mucosa, and T1b when the tumor invades the submucosa. This chapter will focus on T1a tumors limited to the mucosal layer.

Adenocarcinoma

Background

Esophageal adenocarcinoma is thought to arise from the background of Barrett's esophagus. Following the replacement of normal squamous epithelium with metaplastic columnar epithelium in the distal esophagus, in a minority of patients the Barrett's segment evolves into a dysplastic epithelium and eventually to cancer [3]. While dysplasia treatment is performed through a variety of endoscopic modalities, management of superficial esophageal adenocarcinoma requires a deeper understanding of the level of invasion and a potential surgical evaluation.

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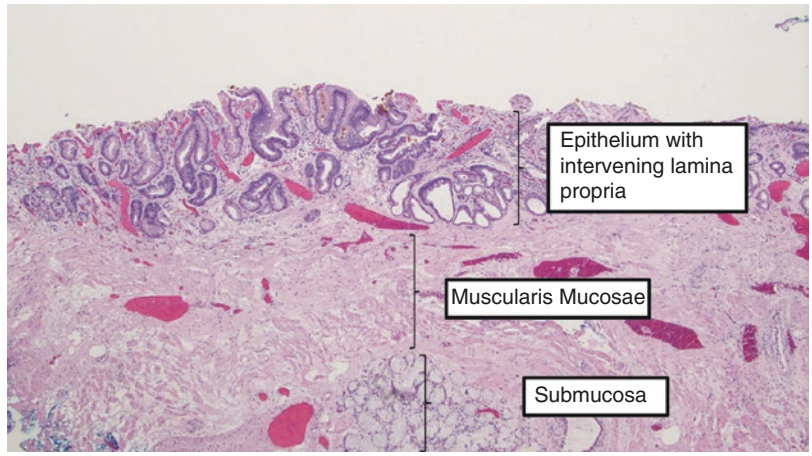

Fig. 5.1 Esophageal wall mucosal layers on hematoxylin and eosin stain

Pretreatment Evaluation

Pretreatment evaluation of esophageal adenocarcinoma, which incorporates locoregional staging and evaluation for distant metastases, guides decision making. Locoregional staging assesses both the degree of extension of the tumor into the esophageal wall as well as the nodal status. Lymph node invasion is incorporated into current staging guidelines and influences long-term prognosis. As tumor depth progresses, so does the risk of lymph node metastasis. For T1a tumors, the risk of lymph node metastasis is estimated to range between 1.3 and 5% [4, 5]. In comparison, this risk increases to up to 27% for T1b adenocarcinoma [6]. Lymphovascular invasion has been determined as the main predictor of lymph node metastasis [7]. Tumor size greater than 2 cm and poor differentiation have also been found to be associated with lymph node metastasis and submucosal invasion [5].

Further staging determination requires imaging to evaluate for local and metastatic disease. Available imaging modalities include computed tomography (CT) scans, positron emission tomography (PET) scans, and endoscopic ultrasound (EUS). CT imaging is recommended as the initial study after the cancer diagnosis is confirmed on histology to evaluate for metastasis [8]. While preoperative staging is addressed elsewhere in this book, it is notable to mention that EUS has the highest staging accuracy for locoregional disease. The accuracy, however, may decline in superficial cancers, and it is debated whether endoscopic mucosal resection (EMR) or other means of staging are more reliable over EUS in this subgroup [9, 10]. According to the most recent statement by the American Gastroenterological Association, if a raised or suspicious area is found in the setting of early adenocarcinoma, a diagnostic EMR is recommended for further evaluation [11].

Treatment Outcomes

Once the tumor is confirmed to be confined to the mucosal layer, current guidelines recommend endoscopic therapy as the preferred therapeutic approach [12]. However, if the T1a lesion demonstrates poor differentiation, lymphovascular invasion, or the resection is incomplete, a surgical option should be explored. The European clinical practice guidelines also recommend endoscopic therapy as the preferred treatment for patients with T1a esophageal adenocarcinoma [13].

EMR has been shown to provide adequate information about the depth of invasion, thus remains an adequate treatment option in mucosal adenocarcinoma. A randomized trial comparing endoscopic submucosal dissection (ESD) to EMR in early Barrett's neoplasia proved both techniques to be highly effective with no significant difference in adverse events between the groups [14]. Current guidelines do not favor one

endoscopic resection technique over another for superficial esophageal adenocarcinoma. In contrast, the most updated European guidelines for mucosal adenocarcinoma treatment favor EMR over ESD as the gold standard [15]. This recommendation stems from a lack of proven superiority of ESD over the EMR method.

Survival outcomes for endoscopically treated T1a cancers are promising. Until recently, esophagectomy was considered the traditional treatment of choice, but evidence continues to mount in favor of endoscopic resection [16]. A recent study followed 1000 patients with mucosal adenocarcinoma treated by EMR over a mean period of 56 months, and found that 93.8% of patients achieved long-term complete remission with a 91.5% 5-year survival rate [17]. In comparison to endoscopic resection, esophagectomy has been found in many studies to have a higher morbidity and mortality. Overall 5-year mortality after esophagectomy for T1a adenocarcinoma is estimated to range from 73 to 80% [6, 18]. However, other studies have revealed no significant difference in 2-year or 5-year T1a-cancer related mortality between the two treatment modalities [19].

Morbidity following esophagectomy surgery has been quoted to be much higher than morbidity after endoscopic resection. Surgical morbidity is reported to be as high as 50%, with respiratory complications being the most common cause [20]. In comparison, major complications following endoscopic resection include bleeding and perforation. The risk of these complications is low, quoted to range from 1.5 to 3% [17, 21]. Other studies have highlighted the risk of dysphagia following EMR. In patients requiring post-resection dilation therapy, the majority still confirmed it to be an acceptable treatment strategy [22]. A study evaluating differences in major complications between endoscopic and surgical resection in patients with T1a adenocarcinoma confirmed no significant events in the endoscopic group versus 32% in the surgical group [23].

Several studies are being performed demonstrating that EMR is an effective minimally invasive treatment strategy for mucosal adenocarcinoma with excellent long-term results [24, 25]. A comparison of patients with intramucosal adenocarcinoma versus high-grade dysplasia demonstrated similar rates of complete eradication and low rates of 5-year recurrence [26]. Endoscopic therapy has also been found to be more cost-effective and to yield more quality-adjusted life years in T1a adenocarcinoma than surgical resection through a modeling analysis [27]. These cumulative findings have influenced current practice patterns. An examination of practice trends revealed that endoscopic therapy for T1a tumors has increased sevenfold from 2004 to 2010, and has become the dominant treatment modality in the United States [4].

Squamous Cell Carcinoma

Background

Squamous cell carcinoma (SCC) incidence has been surpassed by adenocarcinoma in the United States. However, it remains the most common form of esophageal cancer worldwide. Alcohol and tobacco use are risk factors for the formation of SCC, which is usually located in the upper and middle third of the esophagus. The risk of invasion and survival rates vary compared to esophageal adenocarcinoma, thus a different staging system has been employed to categorize these tumors and guide treatment [2]. The most updated TNM clinical staging classification for SCC incorporates histological grade and tumor location into its structure.

Pretreatment Evaluation

A comprehensive assessment of predictive markers and metastatic risk allow for the development of a therapeutic strategy. A study of superficial SCC metastatic prevalence demonstrated a gradual increase in lymph node metastasis with progressive tumor depth [28]. SCC limited to the mucosa has been shown to have an 8–15% risk of pathological lymph node metastasis [28, 29]. Several studies subdivided T1a tumors by depth of invasion, with m1 cancer invading the epithelium, m2 lesions invading the lamina propria, and

m3 tumors extending into the muscularis mucosa [28, 30]. This subdivision highlighted differences between the groups, with no signs of lymph node metastasis until the m3 level was reached.

Treatment Outcomes

Current oncology clinical practice guidelines for early esophageal carcinoma recommend a multidisciplinary evaluation and EMR for T1a tumors without lymph node metastasis, lymphovascular invasion or poor differentiation, regardless of tumor type [31]. Studies have shown EMR to be an effective minimally invasive option in the treatment of superficial SCC [32]. In comparison, European practice guidelines strongly recommend ESD over EMR for the removal of mucosal SCC [13, 15].

The most important feature of a successful resection lies in the en bloc technique, which permits close evaluation of histologic features. If EMR with an en bloc resection is employed to remove small SCC lesions under 15 mm, no difference in local recurrence was found between this technique and ESD [33]. However, for lesions larger than 15 mm, ESD was found to perform better. Overall, for larger lesions EMR may be considered, however ESD should be regarded as the first treatment option. In a retrospective cohort study of early SCC of the esophagus, the rate of recurrence was significantly lower in those who underwent ESD over EMR [34]. A meta-analysis comparing ESD to EMR demonstrated better curative resection rates in the ESD group for esophageal neoplasms [35].

Good survival rates have been documented for T1a SCC tumors, with a 5-year overall survival calculated at over 95% [28]. Tumor invasion depth has been shown to be the main variable affecting survival. A prospective study of patients with T1a SCC who underwent surgical resection demonstrated a 94.3% 5-year survival and a 100% 5-year disease specific survival [36]. A few small studies of patients with early esophageal SCC undergoing ESD highlighted excellent disease-specific survival of 95.8–100% with mean follow-up of 3 years [37–39]. Comparing patients with early esophageal SCC undergoing surgical versus endoscopic resection, long-term survival and cancer-specific mortality was found to be equivalent [40].

No significant differences in procedure-related morbidity have been found between EMR and ESD [41]. Moreover, the frequency of perforation was also not found to be significantly different between the two groups [34]. Of note, this finding may expectedly vary based on operator experience. Several of these studies have originated in centers where ESD is a commonly employed therapy.

Endoscopic Resection Modalities

Endoscopic resection can be achieved through a number of different techniques. These include endoscopic mucosal resection using the cap-assisted, band-assisted, or injection-assisted technique, or by endoscopic submucosal dissection. The choice of modality is guided by lesion histology, size, contour, and operator experience.

Endoscopic Mucosal Resection

EMR can be employed for either diagnosis or treatment of T1a cancer, and provides useful information about the depth of invasion permitting accurate histologic staging. The cap-assisted EMR technique utilizes a cap at the end of the endoscope into which tissue is suctioned (Fig. 5.2). A variety of caps can be used with different diameters and either a straight or oblique shape. Prior to suctioning, the submucosa is frequently injected to provide a lift. Once in position, a snare is used to resect the lesion through electrocautery.

The second method employs a band ligator device, similar to the variceal banding technique (Fig. 5.3). The lesion is suctioned into the cap and a band is deployed around the base of the lesion creating a pseudopolyp. Subsequently, a snare loops around the pseudopolyp base and resection is performed. An advantage of this

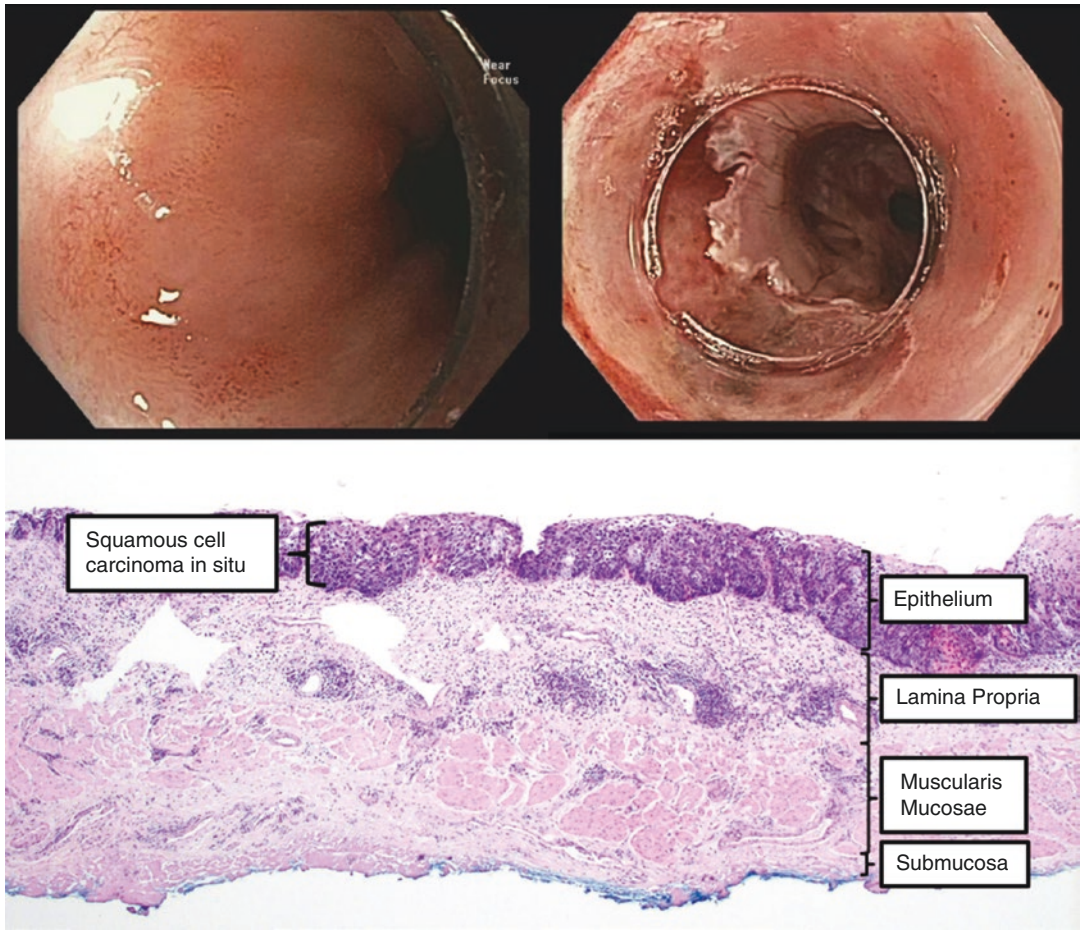

Fig. 5.2 Squamous carcinoma in situ excised by cap-assisted endoscopic mucosal resection

technique is that it does not require a submucosal injection. The multiband mucosectomy device allows for the use of up to six bands in a single session.

Finally, the least-often utilized method involves injecting saline with or without epinephrine into the tissue underlying the lesion. Once the area is raised, a barbed snare is engaged to resect the tissue. The goal of the submucosal injection is to provide a cushion underneath the targeted area, aiding the resection and minimizing perforation risk. Of note, there are currently no FDA-approved submucosal injection solutions for EMR.

A comparison of the two most commonly used techniques in early stage esophageal cancer, the cap-assisted and ligation-assisted modalities, demonstrated similar efficacy and safety [42, 43]. Additionally, no significant difference in perforation risk has been found between the techniques [44]. With no superior EMR method being recognized, currently the choice of therapeutic modality is left to the endoscopic operator.

Endoscopic Submucosal Dissection

ESD utilizes a specialized needle-knife to dissect through the submucosal layer (Fig. 5.4). First, a solution is injected into the submucosa to create a cushion. Throughout the procedure, multiple injections are often required to maintain adequate lift. Following the injection, submucosal dissection is performed until the entire lesion is

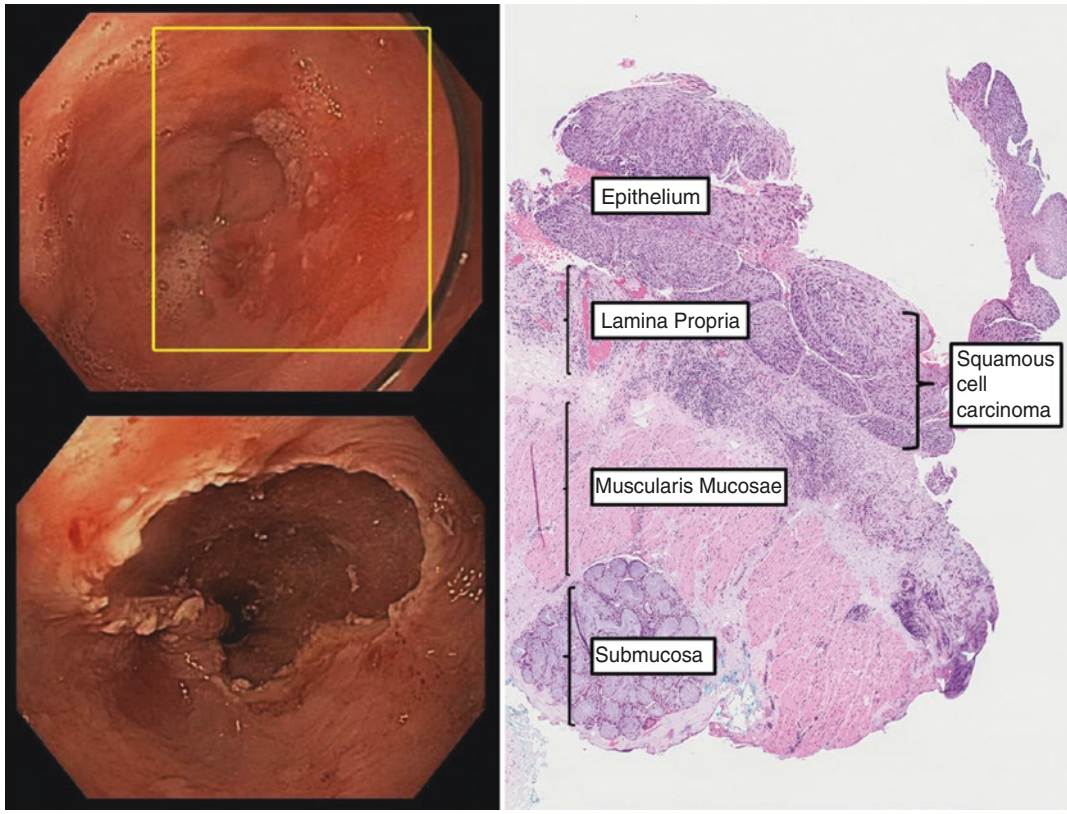

Fig. 5.3 Invasive intramucosal squamous cell carcinoma excised by multi-band endoscopic mucosal resection

removed. Coagulation is often utilized during ESD to provide hemostasis.

As the resection is performed through the submucosal layer, ESD benefits include a more complete assessment of the lesion's margins and the possibility of an en-bloc resection. Studies have demonstrated that it is a safe and effective technique when performed by expert endoscopists [45, 46]. However, this technique requires sub-specialized training, and being a more complex approach, may not be available at most centers. Procedure time has also been found to be substantially lengthier for ESD than for EMR.

Ablative Therapy

Following endoscopic resection of T1a adenocarcinoma, endoscopic ablation of the entire Barrett's esophagus segment should be performed [12]. This multimodal approach has been found to decrease the risk of recurrence. Successful ablation is confirmed when surveillance biopsies demonstrate total dysplasia eradication. Given its safety, efficacy, and cost profiles, radiofrequency ablation has become the preferred ablative modality [12].

In patients treated with EMR along with ablation compared to those treated with EMR alone, neoplasia recurrence rates decreased from 28.3 to 16.5% [47]. Furthermore, combining ESD with RFA ablation in patients with neoplastic Barrett's esophagus achieves high rates of complete remission and lowers the risk of recurrence [48]. Citing similar benefits, current European guidelines advise ablation of the remaining Barrett's segment following endoscopic resection [15]. In comparison to adenocarcinoma, mucosal squamous cell carcinoma that is completely excised may not require post-resection ablation [31].

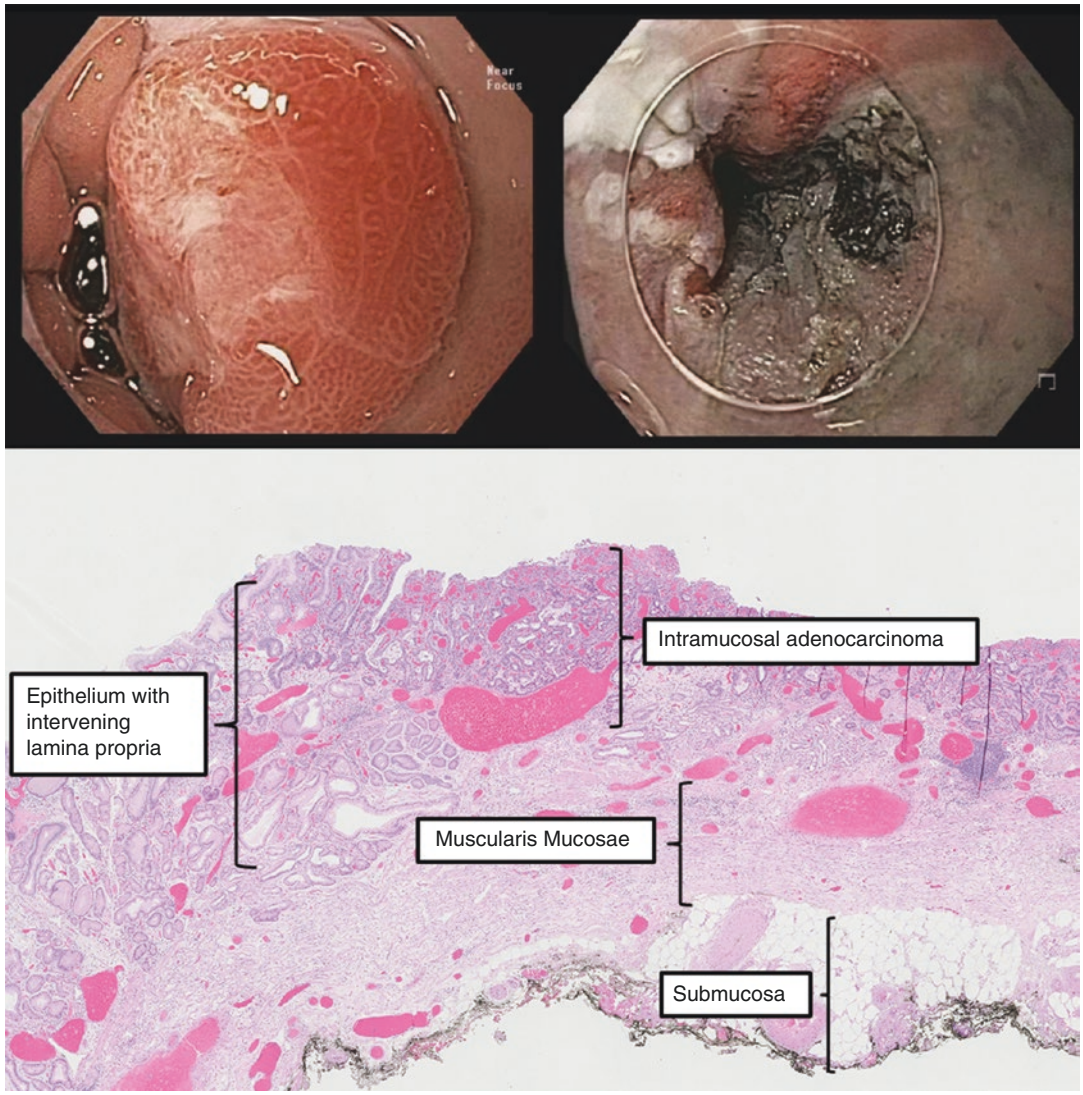

Fig. 5.4 Intramucosal adenocarcinoma at gastroesophageal junction excised by endoscopic submucosal dissection

Conclusions

Endoscopic resection has been proven to be a safe and effective treatment option for superficial esophageal cancer. Existing clinical practice guidelines have been updated according to the most recent literature to recommend endoscopic resection for mucosal esophageal adenocarcinoma. The preferred treatment for mucosal squamous cell carcinoma is also through endoscopic resection, with en bloc resection being the favored method. Given the small but existing risk of recurrence and evolving understanding of the disease, close collaboration between endoscopists, surgeons and oncologists is crucial to provide the highest standard of care. Therapy should be tailored to each individual patient to minimize morbidity and offer the most effective treatment option.

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6 Neoadjuvant and Adjuvant Therapy

Megan Greally and Geoffrey Y. Ku

Introduction

Esophageal cancer is a highly lethal malignancy which occurs less frequently in the United States (U.S.) than in other geographic regions. It accounted for 15,690 deaths in 2017, and is the seventh leading cause of death in American men [1]. It is a major contributor to the cancer burden worldwide and is endemic in parts of East Asia where over half of the approximately 500,000 cases per year worldwide develop [2].

Adenocarcinomas account for 75% of cases in the US following an increase of 4–10% per year in men since the mid 1970s and a steady decline in the number of cases of SCC (attributed to decreased tobacco and alcohol consumption) [3, 4]. Adenocarcinomas have increased in frequency due to increased incidence of gastroesophageal reflux disease and obesity [5].

Neoadjuvant Chemotherapy

Data from the U.K. phase III MAGIC trial led to peri-operative chemotherapy being adopted as the principal approach in Europe and the U.S [6]. This trial evaluated three cycles each of pre- and post-operative operative ECF [epirubicin/cisplatin/5-fluorouracil (5-FU)] and surgery or surgery alone. Of 503 patients, 15% and 11% had gastroesophageal junction (GEJ) and lower esophageal tumors respectively. Peri-operative chemotherapy resulted in significant improvement in 5-year overall survival (OS; 36% vs. 23%, $p = 0.009$), establishing this regimen as a standard-of-care.

More recently, the French FFCD 9703 trial randomized 224 patients with esophagogastric carcinoma to six cycles of 5-FU/cisplatin followed by surgery vs. surgery alone [7]. A significant improvement in 5-year disease-free survival (DFS; 34% vs. 19%, $p = 0.003$) and OS (38% vs. 24%, $p = 0.02$) was detected. While cross-trial comparisons are made with caution, the survival benefit is similar to that observed with ECF in the MAGIC study, raising questions about the benefit of the anthracycline.

The U.K. MRC OEO-5 study randomized 897 patients with esophageal/GEJ adenocarcinomas to pre-operative chemotherapy with 6 weeks of 5-FU/cisplatin or 12 weeks of ECX (epirubicin/cisplatin/capecitabine) [8]. While an improved pathologic complete response (pCR) was observed in the ECX group vs. the 5-FU/cisplatin group (11% vs. 3%), there was no difference in median progression-free survival (PFS) or OS between groups. These results also challenge the convention that anthracycline provides additional benefit and raise uncertainty regarding the optimal duration of neoadjuvant therapy as 6 weeks

M. Greally · G. Y. Ku (✉)
Gastrointestinal Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA
e-mail: greallym@mskcc.org; kug@mskcc.org

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of pre-operative chemotherapy conveyed the same survival benefit as 12 weeks. Furthermore, the CROSS study, (discussed later) found an absolute improvement in OS in the range of 10–15% as seen in other positive phase III studies, despite only receiving 5 weeks of carboplatin/paclitaxel [9, 10]. In addition, only 40–50% of patients in the MAGIC and FFCD studies received or completed adjuvant therapy following surgery indicating that patients benefit from shorter durations of chemotherapy.

Preliminary results of the FLOT4-AIO phase III trial were recently presented in abstract form [11]. This study randomized 716 patients with resectable gastric or GEJ adenocarcinoma to perioperative FLOT (5-FU/oxaliplatin/docetaxol) or ECF/ECX. FLOT was superior to ECF/ECX in all efficacy endpoints including curative resection rates, PFS and OS (median OS 50 vs. 35 months; 5-year OS 45% vs. 36%, HR 0.77, $p = 0.012$). Benefit was seen across all subgroups and the rate of adverse events was similar between groups. Therefore, while there is no benefit to addition of an anthracycline in this setting, there appears to be benefit for a docetaxel-containing 3-drug regimen. Furthermore, only half of patients completed all planned chemotherapy, again highlighting the difficulty in administering adjuvant therapy and suggesting that future clinical trials should focus on evaluating pre-operative approaches.

While the results of FLOT4 have established a new standard-of-care, other phase III studies evaluating pre- or peri-operative chemotherapy in esophagogastric adenocarcinoma have shown less favorable results. The North American Intergroup 113 trial randomized 440 patients to pre-operative 5-FU/cisplatin or immediate surgery. No significant difference in survival was detected. About half of the patients had adenocarcinoma [12]. The MRC OE2 trial of surgery with or without preoperative cisplatin/5-FU enrolled 802 patients and reported a modest improvement in 5-year OS with pre-operative therapy (23% vs. 17%, $p = 0.03$) [13]. Two-thirds of patients had adenocarcinomas and 75% had distal esophagus or gastric cardia tumors. The data are summarized in Table 6.1.

A meta-analysis of ten randomized studies evaluating pre-operative chemotherapy for esophageal/GEJ carcinoma demonstrated a 13% reduction in all-cause mortality in patients with adenocarcinoma compared to surgery alone (HR 0.87, 95% CI 0.79–0.96, $p < 0.005$) [14]. There was a non-significant trend toward benefit in patients with SCC (HR 0.92, 95% CI 0.81–1.04, $p = 0.18$).

Pre-operative Chemoradiation

Several randomized trials, outlined in Table 6.2, have evaluated preoperative chemoradiation vs. surgery alone in esophageal cancer. Of six contemporary studies [9, 15–19], three have demonstrated a survival benefit with preoperative chemoradiation.

The Dutch CROSS trial was a well conducted phase III study which enrolled 366 patients with esophageal tumors; 75% had adenocarcinoma. Over 80% had T3/4 tumors and 65% were node positive by endoscopic ultrasound [9]. Pre-operative radiation (41.4 Gy) with weekly carboplatin/paclitaxel for 5 weeks was compared to surgery alone and resulted in higher R0 resection rates (92% vs. 67%, $p < 0.001$), a pCR rate of 29% (adenocarcinoma 23%; SCC 49%) and improved 5-year OS (58% vs. 44%, $p = 0.003$). There was no increased post-operative mortality in the chemoradiation group. Patients with SCC appeared to derive greater benefit than those with adenocarcinoma (univariate HR for death 0.45 vs. 0.73). However, long-term follow-up confirmed a clinically relevant OS benefit for patients with both histologies [10]. This regimen became a standard-of-care.

Carboplatin/paclitaxel is a convenient, well-tolerated regimen and associated with the highest pCR rate for SCC to date in a phase III trial. The pCR rate for adenocarcinoma compares favorably to other studies. However, it remains unclear if carboplatin/paclitaxel is the optimal regimen to combine with radiotherapy in this setting. CALGB 80803 provides some insight in this regard [20]. This study randomized 257 patients with esophageal/GEJ adenocarcinoma, to receive

Table 6.1 Results of phase III pre- or peri-operative chemotherapy trials in esophageal/GEJ cancer

Treatment	Histology	No. of patients	R0 resection rate	Pathologic complete response rate	Survival		Local failure	Reference
					Median (months)	Overall		
Peri-op ECF + surgery	Adeno	250	69%	0%	**24**	5-year **36%**	14%	Cunningham et al. [6]
Surgery		253	66%	N/A	**20**	5-year **23%**	21%	
Peri-op 5FU/ Cis + surgery	Adeno	109	**87%**	NS	NS	5-year **38%**	24%	Ychou et al. [7]
Surgery		110	**74%**	N/A	NS	5-year **24%**	26%	
Pre-op ECX + surgery	Adeno	446	66%	**11%**	26.1	3-year 42%	NS	Alderson et al. [8]
Pre-op 5FU/ Cis + surgry		451	59%	**3%**	23.4	3-year 39%	NS	
Peri-op FLOT + surgery	Adeno	356	**84%**	NS	**50**	**45%**	NS	Al-Batran et al. [11]
Peri-op ECF/ ECX + surgery		360	**77%**	NS	**35**	**36%**	NS	
Peri-op 5FU/ Cis + surgery	Adeno (54%) + SCC	213	62%	2.5%	14.9	3-year 23%	32%	Kelsen et al. [12]
Surgery		227	59%	N/A	16.1	3-year 26%	31%	
Pre-op 5FU/ Cis + surgery	Adeno (66%) + SCC	400	**60%**	NS	**16.8**	5-year **23%**	19%	Medical Research Council [43] Allum et al. [13]
Surgery		402	**54%**	N/A	**13.3**	5-year **17%**	17%	

Adeno adenocarcinoma, *Cis* cisplatin, *ECF* epirubicin, cisplatin, 5-fluoruoracil, *ECX* epirubicin, cisplatin, capecitabine, *N/A* not applicable, *NS* not stated
Numbers in **bold** indicate statistically significant differences

Table 6.2 Results of phase III pre-operative chemoradiation trials in esophageal/GEJ cancer

Treatment	Histology	No. of patients	R0 resection rate	Pathologic complete response rate	Survival		Local failure	Reference
					Median	Overall		
Preop CRT	Adeno (76%) + SCC	50	45%	24%	16.9 months	3-year 30%	19%	Urba et al. [17]
Surgery		50	45%	N/A	17.6 months	3-year 16%	42%	
Preop CRT	Adeno	58	NS	25%	**16 months**	3-year **32%**	NS	Walsh et al. [18]
Surgery		55		N/A	**11 months**	3-year **6%**		
Preop CRT	SCC	143	81%	26%	18.6 months	5-year 26%	NS	Bosset et al. [15]
Surgery		139	69%	N/A	18.6 months	5-year 26%		
Preop CRT	Adeno (63%) + SCC + other	128	**80%**	9%	22.2 months	NS	15%	Burmeister et al. [16]
Surgery		128	**59%**	N/A	19.3 months		26%	
Preop CRT	Adeno (75%) + SCC	30	NS	40%	**4.5 years**	5-year **39%**	NS	Tepper et al. [19]
Surgery		26		N/A	**1.8 years**	5-year **16%**		
Preop CRT	Adeno (74%) + SCC	178	**92%**	29%	**49.4 months**	5-year **47%**	NS	Van Hagen et al. [9] Shapiro et al. [10]
Surgery		188	**69%**	N/A	**24.0 months**	5-year **33%**		

Adeno adenocarcinoma, *CR, NS* not stated, *Preop CRT* preoperative chemoradiation
Numbers in **bold** indicate statistically significant differences

induction FOLFOX6 (infusional 5-FU/leucovorin/oxaliplatin) or carboplatin/paclitaxel for 5–6 weeks followed by a [^{18}F]2-fluoro-deoxy-D-glucose positron emission tomography (FDG-PET) scan. PET-responders continued with the same regimen during concurrent chemoradiation and non-responders crossed to the other chemotherapy regimen with radiation prior to surgery. Preliminary results of this study are discussed below. The pCR rate in the PET responders to induction FOLFOX who also received FOLFOX with radiation was 37.5% compared to 12.5% in the PET responders to induction carboplatin/paclitaxel who received this regimen with radiation. Both treatments were well-tolerated. While the study was not designed to detect a difference in outcome between regimens, these results are hypothesis-generating.

Other completed randomized trials are associated with methodological concerns (including the lack of meticulous pre-treatment staging) and enrolled small numbers of patients. Debate continues regarding their interpretation. Cumulatively, these studies demonstrate higher R0 resection rates and improved local control. Pre-operative chemoradiation was associated with a 25% reduction in all-cause mortality (HR 0.75; 95% CI 0.59–0.95, p = 0.02) in patients with adenocarcinoma histology and 20% (HR 0.80; 95% CI 0.68–0.93; p = 0.004) in patients with squamous histology vs. surgery alone in the previously discussed meta-analysis [14].

Pre-operative Chemoradiation for Early Stage Disease

In contrast to patients with locally advanced disease, the management of patients with earlier stage disease is less well defined.

The French FFCD 9901 study did not demonstrate a benefit in disease-free or OS for pre-operative chemoradiation vs. surgery alone in 195 patients with stage I or II esophageal/GEJ carcinoma [21]. A majority of patients (72%) had SCCs. The R0 resection rate in the surgery-alone arm was 93% and this was not enhanced with pre-operative chemoradiation. In-hospital post-operative mortality was increased in the chemoradiation arm (11.1% vs. 3.4%, p = 0.049) which may have obscured any small survival benefit from chemoradiation. Current guidelines from the National Comprehensive Cancer Network recommend upfront surgery for patients with cT1N0 tumors.

Pre-operative Chemoradiation vs. Chemotherapy

The German POET study randomized 119 patients with GEJ adenocarcinomas to 5-FU/leucovorin/cisplatin followed by surgery or 5-FU/leucovorin/cisplatin followed by chemoradiation with cisplatin/etoposide and then surgery [22]. Due to poor accrual, its power to detect a difference between groups was limited. Patients who received chemoradiation had a higher pCR rate (15.6% vs. 2%, p = 0.03) and a trend toward improved local control (76.5% vs. 59%, p = 0.06) and 3-year OS (47.4% vs. 27.7%, p = 0.07).

The meta-analysis discussed above reported a non-significant trend toward improvement in all-cause mortality with pre-operative chemoradiation over chemotherapy (HR 0.88; 95% CI 0.76–1.01, p = 0.07) [14].

The most compelling justification favoring pre-operative chemoradiation over chemotherapy is the signal of improvement in R0 resection rates for GEJ tumors. The R0 resection rates reported in MAGIC and OEO-5 were <70% while patients who received chemoradiation in CROSS had R0 resection rates >90%.

Intensification of Combined Modality Therapy

FDG-PET imaging is an increasingly well-defined tool to assess response to therapy. A number of studies have shown that the degree of response detected by PET following pre-operative chemoradiation [23, 24] or chemotherapy [25, 26] correlates with pathologic response at surgery and survival.

The MUNICON phase II trial demonstrated that among patients with locally advanced GEJ adenocarcinomas who underwent PET imaging after 2 weeks of induction 5-FU/cisplatin, patients who were PET responders (defined as ≥35% reduction in standard uptake value between baseline and repeat scans) had a significantly better prognosis than non-responders [27].

The role of PET in tailoring chemoradiation after induction chemotherapy has been explored. A retrospective review of 201 patients with esophageal/GEJ adenocarcinomas where PET non-responders were switched to alternative chemotherapy during radiation suggested that improvements in pCR rate and PFS are achievable. A trend toward improved OS was observed [28].

Preliminary results of CALGB 80803 indicated improvement in the pCR rate in PET non-responders who changed chemotherapy to 17% (carboplatin/paclitaxel switched to mFOLFOX6) and 19% (mFOLFOX6 switched to carboplatin/paclitaxel) [20], compared to a historical rate of 3% in the retrospective analysis above. Survival data are awaited. The study met its primary endpoint and suggests that early response assessment should be incorporated into future studies evaluating neoadjuvant therapy.

Definitive Chemoradiation

Two randomized studies have compared definitive chemoradiation with chemoradiation followed by surgery and results support a non-surgical approach in select patients [29, 30]. Despite improved local control, neither trial demonstrated improved survival with surgery. The majority of patients had SCC and definitive chemoradiation is a reasonable approach in these patients when an endoscopic complete response is achieved, and especially for those who are not surgical candidates.

The FFCD 9102 study provides some insight as to whether patients who do not respond to initial chemoradiation with cisplatin/5-FU benefit from subsequent surgery. Responding patients were randomized to surgery vs. further chemoradiation. Of 451 patients, 192 were not randomized to further protocol therapy (due to poor response, medical contraindications or patient refusal) [31]. Of the 192 patients, 112 underwent surgery and their median OS was significantly superior to patients who did not undergo surgery (17.0 vs. 5.5 months, $p < 0.0001$) and was comparable to the median OS of the patients who were randomized (18.9 months, $p = 0.40$). While this data must be interpreted cautiously, it suggests that salvage esophagectomy may be beneficial for patients who do not respond to chemoradiation.

Patients with adenocarcinoma have lower rates of pCR after chemoradiation and there are no randomized data demonstrating that definitive chemoradiation is comparable to chemoradiation and surgery. However, patients with high operative risk who obtain a clinical complete response to chemoradiation may undergo close surveillance. A salvage esophagectomy can be considered in those with local relapse, although operative complications may increase when surgery is delayed >6–8 weeks following chemoradiation. However, three studies have reported no significant deterioration in outcomes in patients who underwent delayed surgery [32–34].

Post-operative Chemoradiation

In the U.S., post-operative chemoradiation is a standard-of-care for GEJ/gastric cancers following upfront resection, predominantly based on the Intergroup 116 study [35]. This trial randomized 556 patients (20% had GEJ tumors) with resected stage ≥IB disease to adjuvant chemoradiation with bolus 5-FU/leucovorin or observation. The 3-year relapse-free survival (48% vs. 31%, $p < 0.001$) and 3-year OS (51% vs. 40%, $p = 0.005$) were significantly improved in the chemoradiation arm. However, 54% had less than D1/D2 resections and chemoradiation potentially compensated for inadequate surgery given that the greatest impact of chemoradiation was a reduction in local recurrence. Radiotherapy may not provide benefit in patients who have optimal surgery.

CALGB 80101 investigated the role of more intensive chemotherapy in 546 patients with gastric cancer (30% had GEJ and proximal stomach tumors) [36]. Patients were randomized to bolus 5-FU/leucovorin preceding and following chemoradiation with infusional 5-FU or ECF before and after chemoradiation with infusional 5-FU. There was no improvement in 5-year DFS (44% vs. 44%, $p = 0.69$) or OS (39% vs. 37%, $p = 0.94$) with ECF vs. 5-FU/leucovorin.

Finally, the Dutch CRITICS trial compared peri-operative ECX or EOX (epirubicin, oxaliplatin, capecitabine) to pre-operative ECX or EOX and adjuvant chemoradiation with capecitabine in 788 patients with gastric and GEJ (17% of patients) adenocarcinoma. Preliminary results demonstrated no difference in PFS or 5-year OS (40.8% vs. 40.9%) between treatments, suggesting that adjuvant chemoradiation is not warranted in patients who have received pre-operative chemotherapy [37].

Only 50–60% of patients in these three studies completed all planned treatment, providing strong rationale for a pre-operative therapy approach.

Post-operative Chemotherapy

Two large phase III East Asian trials have demonstrated a survival benefit for post-operative chemotherapy alone in patients with gastric carcinoma [38, 39]. Both studies included a small minority of patients with GEJ tumors and it is unclear whether these data can be extrapolated to the patient population discussed here.

Two Japanese studies have evaluated adjuvant cisplatin/vindesine [40] and 5-FU/cisplatin (JCOG 9204) [41] respectively in patients with resected esophageal SCC. Neither treatment improved survival; however, an unplanned subset analysis of JCOG 9204 demonstrated a survival benefit for patients with lymph node involvement (5-year DFS 52% vs. 38%). Subsequently, JCOG 9907 randomized 330 patients with esophageal SCC to 2 cycles of pre- or post-operative 5-FU/cisplatin [42]. Pre-operative chemotherapy improved 5-year OS (55% vs. 43%, $p = 0.04$) vs. post-operative therapy. However, only 58% of the patients randomized to post-operative therapy received any treatment and 23% of the patients randomized to this arm of the study had pN0 disease and did not receive post-operative therapy, per protocol, based on prior data that adjuvant therapy only benefited patients with lymph node positivity. In addition, pre-operative chemotherapy was associated with a survival benefit only in N0 patients in this study, contrasting with JCOG 9204, which reported a benefit only in N1 patients.

Conclusions

The treatment of locally advanced esophageal carcinoma has evolved over the last 15 years and multiple phase III trials clearly demonstrate that multimodal therapy improves outcomes. Several trials have demonstrated a survival benefit for the addition of pre-operative chemoradiation to surgery in patients with esophageal/GEJ tumors. The use of FDG-PET to tailor chemotherapy during radiation is a promising strategy. While peri-operative chemotherapy is a treatment option for GEJ adenocarcinomas, recent studies have shown suboptimal R0 resection rates with this approach. Definitive chemoradiation is standard-of-care in patients who are not surgical candidates and in patients with SCC who obtain a clinical complete response.

Adjuvant chemoradiation is an option in patients with resected esophageal/GEJ adenocarcinoma. While adjuvant chemotherapy alone is associated with improved outcomes in East Asian studies, it is unclear if these data can be extrapolated to patients with GEJ tumors. There remains no proven benefit for chemotherapy alone in patients with resected SCC.

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7 Restaging After Neoadjuvant Therapy

Smita Sihag and Tamar Nobel

Introduction

Esophageal cancer is the eighth most common cancer worldwide and affects over 450,000 individuals annually [1]. The vast majority of patients with newly diagnosed malignancies of the lower esophagus and gastroesophageal junction (GEJ) harbor advanced disease at the time of presentation; and unfortunately, the onset of symptoms such as dysphagia often correlate with tumor depth and indicate deeper penetration (into the muscularis layer) [2]. Although surgical resection remains the mainstay of curative treatment for esophageal cancer, neoadjuvant multimodality therapy with chemotherapy and radiation prior to surgical resection has been demonstrated to improve survival in patients with locally advanced disease [3].

The optimal approach to neoadjuvant therapy remains controversial. On the basis of the OEO2 trial (2002), it is standard practice in the United Kingdom to administer neoadjuvant chemotherapy (nCT) alone prior to surgical resection [4, 5]. The MAGIC trial (2006), which randomized patients to perioperative chemotherapy (epirubicin, cisplatin, fluorouracil) plus surgery versus surgery alone, provided further support for this approach [6]. While no patients exhibited a pathological complete response (pCR) to neoadjuvant chemotherapy in this trial, there was evidence of tumor shrinkage and/or down-staging in a higher proportion of patients in the chemotherapy group. The addition of radiation prior to tumor resection may increase achievement of R0 resection and reduce local recurrence. The CROSS trial (2012) established the current standard of practice in the United States [7]. The study compared concurrent neoadjuvant chemoradiation therapy (nCRT), consisting of carboplatin/paclitaxel and 41.4 Gy of radiation followed by surgery, to surgery alone. In this study, a pCR was achieved in 47 (29%) out of 161 patients total; 28/121 (23%) of patients with esophageal adenocarcinoma (EAC) and 18/37 (49%) of patients with esophageal squamous cell carcinoma (ESCC). Although there remains no definitive answer as to the best approach, the case for neoadjuvant treatment in locally advanced esophageal cancer is demonstrated by these well-executed randomized trials demonstrating improved outcomes with both nCT and nCRT, as well as several recent meta-analyses [3, 8]. However, the results of these studies also demonstrate that only a subgroup of patients with esophageal cancer benefit from neoadjuvant therapy.

Evaluation of response to neoadjuvant treatment through restaging has two primary goals. First, and most importantly, is the detection of disease progression that may preclude resectability. If unresectable metastatic disease is found, palliative management is appropriate. The second

S. Sihag (✉) · T. Nobel
Memorial Sloan Kettering Cancer Center,
New York, NY, USA
e-mail: sihags@mskcc.org; nobelt@mskcc.org

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objective is the assessment of treatment response as multiple studies have demonstrated that both tumor regression and pCR portend an improved prognosis. Pathologic response, and especially pCR, has been demonstrated to be the most important determinant of disease free survival (DFS) and overall survival (OS) after neoadjuvant therapy. In a previous series from our institution, patients with pCR were demonstrated to have a 5-year survival of up to 60% and were almost twice as likely to have DFS during that period [9]. Additionally, it has been suggested that patients with a significant response to neoadjuvant treatment may be spared esophagectomy. As such, the ability to predict exceptional treatment responders has tremendous value for determination of prognosis and therapeutic decision-making.

Unfortunately, the accuracy of currently available diagnostic tools to identify pCR after neoadjuvant treatment remains disappointingly low. Given these limitations, esophagectomy is still strongly preferred in surgical candidates for lower esophageal and junctional tumors regardless of histology. The current standard for restaging as defined by the National Comprehensive Cancer Network (NCCN) guidelines recommends the use of integrated 18-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) imaging 5–8 weeks following the completion of neoadjuvant therapy [10]. Below we provide a review of currently available modalities and discuss the rationale for these guidelines.

Role of Endoscopy in Restaging

Endoscopic biopsy and ultrasound play a vital role in the initial diagnosis and staging of esophageal cancer. However, current evidence suggests that repeat endoscopy following neoadjuvant treatment is rarely indicated.

Endoscopic Biopsy

Endoscopic biopsy is the standard approach to the diagnosis of esophageal cancer. Similarly, biopsy after nCRT may be used to check for presence of residual tumor prior to surgical treatment. This approach is limited by the risk of sampling bias and the superficial nature of the specimen obtained, which may miss deep residual tumor [11]. The drawbacks for this diagnostic tool are supported by several studies demonstrating the poor ability of this modality to predict pathologic response after treatment. In a series of 65 patients, Yang et al. investigated the use of endoscopic biopsy in predicting rates of pathologic after nCRT [11]. The majority of patients with a negative biopsy were found to have residual disease on surgical pathology (77%), raising significant concerns with the use of this technique. A negative biopsy was associated with absence of residual disease in only 23% of patients. In contrast, 92% of patients with a positive biopsy had residual disease, and a positive result predicted increased likelihood of residual nodal metastatic disease, suggesting that a positive biopsy has the potential for prognostic importance. In a 2008 study of 165 patients, Sarkaria et al. similarly reported that a negative post-nCRT biopsy was associated with pCR in only 31% of patients [12]. A negative biopsy was more predictive of pCR for patients with ESCC compared to EAC ($p < 0.001$). Although no survival benefit was demonstrated with negative biopsy, this finding did correlate with greater treatment response and tumor downstaging. More recently, a study of 189 patients with ESCC demonstrated that 36% of patients with a negative biopsy after nCRT still had residual disease [13]. The 5-year OS in patients with a negative biopsy was higher than that of patients with a positive biopsy (48.3% vs 21.8%, respectively), most likely reflecting the impact of pathologic tumor regression. The results of these studies suggest that negative biopsy may still be associated with a clinically significant rate of residual disease on final pathology which limits the diagnostic role of this test; however, these observations do vary with histology type. In patients with ESCC, a higher probability of treatment response contributes to the observed higher correlation between cCR and pCR.

The etiology of the high false negative rates on post-nCRT endoscopic biopsy is multifactorial; in part, it may be explained by: (1) radiation induces

changes to the esophageal mucosa leading to increased sampling error, and (2) reluctance by endoscopists to perform aggressive biopsies due to the associated increased risk of the procedure in a previously irradiated field and the observation that biopsy results do not alter usual clinical management [14]. Several factors, including endoscopic findings and timing on post-nCRT biopsy, have been proposed as adjuncts to improving the diagnostic accuracy of this test. Chao and colleagues performed a retrospective review of 227 patients with ESCC treated with neoadjuvant chemoradiation [15]. Amongst 135 patients with a negative biopsy result, 37% had no residual disease on pathology. The type of residual lesion identified on endoscopy was significantly associated with the predictive value of a negative biopsy; as such, they observed that the negative predictive value of a negative biopsy was 77.8% when the esophagus appeared "normal", but dropped significantly in the presence of ulceration or stricture (30.3% and 23.1%, respectively). More recently, the same authors investigated the correlation between timing and accuracy of endoscopic biopsy in 213 patients with ESCC [14]. Accuracy increased when the procedure was performed at or after 45 days after time of nCRT completion. Increased accuracy with a longer time interval may be the result of greater resolution of radiation-induced inflammation.

Although certain observed patient and endoscopic characteristics may help improve the diagnostic capabilities of endoscopic biopsy post-nCRT, evidence is lacking to support regular use. A summary of studies evaluating the ability of endoscopic biopsy to predict residual disease is given in Table 7.1.

Endoscopic Ultrasound

Endoscopic ultrasound (EUS) is considered the most accurate method for assessing depth of tumor invasion and regional lymph node involvement on routine pre-treatment clinical staging in esophageal cancer patients. In the context of restaging, the benefit of EUS is less apparent as the addition of EUS to endoscopic biopsy demonstrates only marginally superior results to biopsy alone. In a recent study of 110 patients, Misra and colleagues evaluated the diagnostic accuracy of EUS post- treatment [16]. EUS accurately predicted both depth of invasion (T) and nodal (N) stage for only 23.6% of patients; however, prediction of N was more accurate than T (58% vs 39%, respectively). The authors observed that overstaging occurred more frequently than understaging, especially with regard to tumor depth; observed T stage was higher in 54% of patients, and lower in only 6% of patients. In a meta-analysis including 16 studies from 1992 to 2013, EUS had limited ability to correctly identify T1, T2 and T4 disease after neoadjuvant therapy (23–43%) but was able to identify 81% of patients with T3 tumors [17]. In determination of N status, the pooled sensitivity and specificity of EUS were only 69% and 52%, respectively.

The utility of restaging EUS is called into question, largely due to the difficulty of distinguishing residual primary tumor from treatment effects, namely inflammation or fibrosis following neoadjuvant radiation. Restoration of the normal esophageal wall architecture is infrequent, even in the setting of tumor regression. Therefore, EUS may be better at restaging tumors with limited treatment response as opposed to those with

Table 7.1 Summary of studies evaluating accuracy of endoscopic biopsy results

Study	N	ESCC/EAC	Negative biopsy (%)	pCR (%)	Accuracy (%)
Shaukat et al. [35]	30	3/27	50	13.3	57
Yang et al. [11]	65	6/57	80	20	35.4
Schneider et al. [36]	80	49/31	69.7	16.7	47
Sarkaria et al. [12]	146	29/117	80.8	26.7	50
Miyata et al. [13]	123	123/0	49.5	22.7	37.4
Chao et al. [15]	227	227/0	59.4	26.4	59.9

Adapted from Chao et al. [15]
ESCC/EAC Esophageal Squamous cell carcinoma/Esophageal adenocarcinoma, *pCR* Pathologic complete response

marked regression. With regard to lymph nodes, assessment by EUS following neoadjuvant therapy utilizing size measurement is only marginally better than flipping a coin. Pathologic assessment via fine needle aspiration (FNA) biopsy may also be unreliable due to the presence of necrosis and inflammation following chemoradiotherapy. At present, we do not believe that EUS should be routinely used in restaging after nCRT.

Role of FDG-PET/CT in Restaging

Most centers currently utilize integrated FDG-PET/CT to stage and restage esophageal cancers in accordance with the NCCN guidelines. While both CT and EUS provide excellent local anatomic visualization of esophageal tumors, integrated FDG-PET/CT is able to add the benefit of functional information and can assist in ruling out distant metastatic disease.

Characterization of Disease Burden

In distinguishing between potentially curable and likely incurable patients, FDG-PET/CT has been shown to have greater efficacy and may add prognostic value to CT and EUS. Cerfolio and coauthors conducted an early prospective trial of 48 patients and compared the accuracy of CT, EUS with FNA biopsy, and integrated FDG-PET/CT. FDG PET-CT was significantly more accurate in determination of nodal disease compared to EUS-FNA and CT alone (93% vs 78% and 78%, respectively) [18]. A study of 55 patients demonstrated that FDG PET-CT was highly effective in the detection of regional and distant recurrence with accuracy of 87.2% [19]. These findings support the recommendations by NCCN pertaining to the use of FDG-PET/CT for assessment of resectability.

Treatment Response and Prognosis

FDG-PET/CT has been demonstrated to have an important role in assessment of tumor response to treatment. Studies utilizing FDG-PET/CT imaging before and after nCRT have proven useful in distinguishing responders from non-responders. Tumor regression has previously been shown to be linked with DFS therefore emphasizing the important prognostic implications of identification of treatment response [20]. With respect to the role of FDG-PET/CT in evaluation of treatment response, relative change in maximum standard uptake value (SUV_{max}) in particular appears to have the greatest predictive capacity. In a study of 77 patients with a pCR rate of 28.6%, patients with pCR had a significantly higher relative delta SUV than patients without pCR (0.6 vs 0.4, respectively; $p = 0.02$) [21]. Delta SUV value of less than 45% was correctly associated with residual disease in 91.7% of patients. Similarly, a retrospective review of 187 patients with locally advanced esophageal cancer at Moffitt Cancer Center showed that while absolute change in SUV after nCRT did not predict tumor regression, increased relative rate in change of SUV was significantly associated with better treatment response ($r = 0.18$, $p = 0.02$) [22]. Patients with a robust metabolic response, i.e. decrease in SUV $\geq$ 70% predominantly demonstrated a favorable pathologic response, and this threshold was associated with a significant increase in overall survival. The idea that metabolic activity and pathologic response are correlated is fairly well established in the literature at this time, though earlier studies were somewhat conflicted perhaps due to differing technologies during that period [23]. Figure 7.1, for example, depicts the limitations of FDG-PET/CT in predicting a pCR. This case is a 73 year-old male who presented with uT3N1 GEJ adenocarcinoma. Prior to nCRT, PET/CT imaging demonstrated an FDG-avid (SUV 5.5) mass of the distal esophagus (Fig. 7.1a,*). After neoadjuvant treatment, complete resolution of metabolic activity of the lower esophageal mass was observed (Fig. 7.1b,*). However, final surgical pathology demonstrated residual T3 disease.

Assessment of metabolic response on FDG-PET may have important prognostic relevance

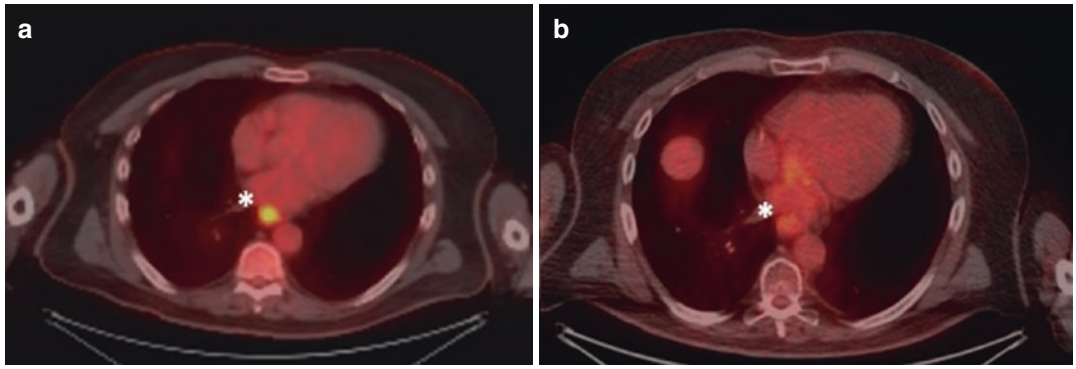

Fig. 7.1 FDG-PET/CT imaging for restaging. (**a**) Before chemoradiation. (**b**) After chemoradiation

as suggested above. A meta-analysis of 26 studies encompassing 1544 patients with locally advanced esophageal cancer showed that complete metabolic response on FDG-PET/CT was associated with significantly increased OS and DFS in comparison with patients demonstrating minimal or no response [24]. However, it is important to note that the studies did differ with respect to neoadjuvant treatment regimen, timing of post-therapy FDG-PET/CT, and methodology used in assessment of metabolic response (relative SUV change, absolute maximum and mean values, and subjective visual assessment or tumor length measurement). It is worth considering that there is likely to be a difference in the efficacy of restaging following chemotherapy vs chemoradiotherapy in terms of the amount of local fibrosis and inflammation that may be present, and the results from study to study may vary based on what type of neoadjuvant therapeutic regimen was administered.

Comparison of FDG-PET/CT to other modalities demonstrates both the benefits and ongoing limitations in the use of FDG-PET/CT. Westerterp and colleagues performed a systematic review of early high-quality studies in 2005 and illustrated the weakness of utilization of CT alone in assessment of treatment response [25]. Maximum joint values for sensitivity and specificity were 54% for CT alone, and relatively equivalent for FDG-PET/CT (86% and 85%, respectively). A more recent study from the United Kingdom also demonstrated that FDG-PET/CT is more sensitive than regular CT in identification of interval disease progression and predicting incurable disease at surgery in 383 patients that were treated with neoadjuvant chemotherapy ($p = 0.005$) [26]. Restaging using a combination of endoscopy with biopsy or EUS and FDG-PET/CT fails to outperform either modality alone. A potential limitation in the use of FDG-PET/CT to assess response to nCRT is in determination of metastatic disease. The accuracy of PET CT in identifying metastatic disease is in the range of 4–8%, based on two studies that investigated this question specifically [27, 28]. Gabriel et al. retrospectively reviewed 283 patients and found a positive predictive value of FDG-PET/CT in detecting metastatic disease to be only 15.6%. Interestingly, 21.6% of patient had false positive findings, mainly in the lung and liver, that were ultimately proven to be biopsy negative, suggesting that a high number of patients received unnecessary additional work-up [27].

PET-Directed Neoadjuvant Therapy

Several institutions have adopted a FDG-PET/CT-directed strategy for determining the optimal chemotherapy regimen to be administered concurrently with radiation in the neoadjuvant setting. At Memorial Sloan Kettering, Ku and colleagues showed that use of this approach resulted in a higher pCR rate (15% vs 3%) among PET responders vs PET non-responders [29]. In

addition, median progression free survival was prolonged from 10.0 months to 18.9 months. A PET responder was defined as having at least a 35% reduction in the maximum standard uptake value of the tumor following induction chemotherapy. The chemotherapy regimen was then either continued or switched based on PET response, and the remainder of treatment was given in conjunction with 50 Gy of radiation for 5 weeks. Goodman et al. recently presented initial results that further support this strategy as part of the Cancer and Leukemia Group B (CALGB) 80,803 Alliance Trial [30].

Ongoing Limitations in Restaging

The above discussion highlights the ongoing difficulties in clinical restaging; use of a combination of endoscopy with biopsy or EUS and FDG-PET/CT fails to obviously out-perform either modality alone. By definition, if no residual disease is detected using a combined approach with endoscopy and radiographic imaging, a so-called clinical complete response (cCR) has been achieved. However, the relationship between cCR and pCR is not strongly supported by available data. In an analysis of a large cohort of 284 patients at MD Anderson Cancer Center, 77% of patients were classified as achieving cCR while only 31% demonstrated pCR on final surgical pathology [31]. Almost all patients with a positive pCR were identified as cCR (97%); however, only 30% of patients without pCR were identified based on clinical findings. In this case, the criteria used to assess cCR included upper endoscopy with negative biopsy plus integrated FDG-PET/CT where the SUV normalized to physiologic background level. The majority of patients in this study (>90%) had EAC on histology with clinical stage II or III disease. Molena et al. from Memorial Sloan Kettering published a study demonstrating a similarly disappointing predictive power of cCR on patients with ESCC treated with trimodality therapy [32]. Restaging tools included CT in 96% of patients, FDG-PET/CT in 57% of patients, and endoscopy in 97% of patients (with biopsy in 52% of patients). Decrease in PET SUV_{max} by >70%, normal appearing endoscopy, and negative biopsy were all significantly correlated with a pCR, although none of these were able to definitively confirm the absence of residual disease in the primary tumor. In a study of 662 patients, 61 demonstrated cCR, as defined by FDG-PET/CT and repeat endoscopic biopsy, and declined surgery with a subsequent relapse-free survival rate of 35% [33]. Given that currently available clinical tools are extremely limited in terms of specificity, especially for detection of pCR, esophagectomy is uniformly recommended.

There is increasing focus on identification of molecular markers that may predict response to nCRT on pretreatment biopsy. Extensive research efforts have been applied to the use of genomic sequencing to identify mutations that help predict treatment response in esophageal cancer. A recent meta-analysis evaluating 46 articles and 56 biomarkers identified low expression of COX2, miR-200c, ERCC1 and TS, or high expression of CDC25B and p16, as potential predictors of response to CT/CRT [34]. These findings have yet to be applied in a standard clinical practice but may help better characterize treatment response and individualize therapeutic interventions in the future.

Conclusions

Restaging for the purposes of ruling out metastatic or unresectable disease using FDG-PET/CT is recommended in accordance with NCCN guidelines despite ongoing limitations in accuracy. FDG-PET/CT allows for differentiation between responders vs non-responders to neoadjuvant therapy, but lacks sufficient sensitivity or specificity to detect a complete response. Restaging via endoscopy or EUS, however, is unreliable and of limited clinical utility. Currently, there remains a need for further development of accurate instruments for prediction of response to neoadjuvant treatment.

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8 Anesthetic Concerns for Esophageal Surgery

Jacob Jackson and Alessia Pedoto

Introduction

Esophageal surgery for cancer can be curative but is associated with significant morbidity and mortality. Scrutinizing the perioperative anesthetic management for the procedure seeks to understand its impact on outcomes and discover opportunities for improvement. Moreover, surgical approaches to esophagectomy continue to evolve with the advent of minimally invasive techniques and robotic surgery, and anesthetic methods and concerns must evolve in parallel.

The anesthesiologist plays a crucial role throughout the perioperative period, ensuring an appropriate preoperative evaluation and optimization of modifiable conditions, intraoperative management, and recovery. For the future, evidenced-based practices are being formalized into enhanced recovery pathways to reduce complications and give patients the best care possible, making the role of the anesthesia provider during the perioperative period more pronounced.

J. Jackson (✉) · A. Pedoto
Department of Anesthesiology and Critical Care Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA
e-mail: jacksoj1@mskcc.org; pedotoa@mskcc.org

Preoperative Evaluation

Initial Assessment and Testing

Patients presenting for esophagectomy may have several comorbidities pertinent to their anesthetic management in addition to their esophageal pathology. Appropriate patient selection and evaluation is necessary to mitigate potential complications of what is already a highly morbid procedure.

Gastroesophageal reflux disease (GERD) and dysphagia are commonly associated with esophageal lesions and predispose to pulmonary aspiration. Severe GERD can cause pharyngolaryngitis, chronic cough, or asthma-like symptoms; chronic aspiration can lead to pulmonary fibrosis.

Smoking and alcohol use should be assessed with consideration for presence of chronic obstructive pulmonary disease (COPD) and hepatic dysfunction, respectively. Active smoking at the time of surgery, especially if combined with excessive alcohol use, is associated with an increase in postoperative complications after esophagectomy, such as decreased wound healing and increased cardiovascular and respiratory events [1]. *Heavy alcohol* users (more than 24 g/day in women, 35 g/day in men) are at increased risk for general morbidity, infections, pulmonary complications, increased hospital length of stay, intensive care unit admission and 30-day mortality. *Acute alcohol withdrawal* can occur within 6–8 h of abstinence, manifesting as hallucinations,

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seizures and status epilepticus. *Delirium tremens* is observed after 48–96 hours and can last up to 2 weeks. Cognitive dysfunction is common in this phase [2]. Risks from smoking and alcohol use may be reversible, depending on the duration of smoking and the interval of abstinence [3].

Poor nutritional status, resulting from the disease state, poor oral intake, or chemoradiation toxicity, decreases physiologic tolerance to the procedure and impairs healing and recovery [4]. Electrolyte impairment and coagulopathy can develop, as well as hypoalbuminemia affecting drug binding. A poor preoperative nutritional status has been associated with a worse postoperative outcome. Parameters used to assess nutrition include albumin, cholesterol and total lymphocyte count [5].

Neoadjuvant chemoradiation is often used in the preoperative period to decrease tumor size, increase the curative success of surgery, and decrease distant micrometastases [6, 7]. *Chemotherapeutic agents* can cause bone marrow suppression with anemia and thrombocytopenia. Anemia increases the chances of red blood cell transfusion with its associated complications. Thrombocytopenia may exacerbate intraoperative bleeding or preclude neuraxial blockade. Platinum derivatives can cause renal dysfunction or impaired hearing [8], while fluorouracil is associated in rare cases with cardiomyopathy, hyperammonemia and encephalopathy [9]. *Immunotherapy*, a successful treatment for melanoma and lung cancer, is being investigated in patients with esophageal tumors, showing some promising results [10]. These drugs specifically target T-cells and their receptors, re-activating the immune system against cancer cells. Their potency seems to be increased after exposure to radiation treatment and because of their mechanism of action, they can activate several immune related side effects within 3–6 months of exposure. The severity is variable and in most cases transient. Skin rashes and diarrhea are the most common side effects. Hypophysitis (0.6–9%), hypothyroidism (20%), diabetes mellitus (0.2–0.9%) and adrenal insufficiency (0.8–1.6%) with secondary hyponatremia have been reported. Hypoparathyroidism with hypocalcemia has also been observed but is extremely rare. Mild cases are usually monitored and managed conservatively, while for severe cases, steroid treatment with thyroid replacement is recommended [11]. Immunotherapy is usually continued unless severe symptoms are present.

After completing a thorough history and physical exam, appropriate *laboratory studies* should include a comprehensive metabolic panel to analyze electrolytes, renal function, and hepatic function, and a complete blood count to quantify anemia and thrombocytopenia, if present. *Coagulation studies* are relevant for patients with a bleeding diathesis or who are taking anticoagulants but also serve to evaluate hepatic function and safety of neuraxial blockade. Severe malnutrition may be associated with abnormal coagulation studies.

Comorbid *cardiovascular disease* can significantly increase patient mortality risk and should be evaluated in accordance with American College of Cardiology/American Heart Association guidelines (ACC/AHA) [12]. *Twelve-lead electrocardiogram* is performed as indicated for patients with known coronary heart disease, significant arrhythmia, peripheral arterial disease, cerebrovascular disease, or other significant structural heart disease, or may be performed as screening for myocardial ischemia or arrhythmia. More invasive cardiac testing (e.g. *stress test, angiogram*) is indicated in patients at high risk (such as unstable angina, decompensated chronic heart failure, arrhythmias and severe valvular disease) when abnormal results are followed by an intervention [12]. Cardiac catheterization is highly recommended if followed by coronary artery revascularization. Patients with and without preexisting cardiac disease have a similar incidence of postoperative major adverse cardiac events (MACE) [13]. However, the former have higher incidence of atrial fibrillation and 30-day postoperative mortality. *Preoperative angina* is associated with a higher incidence of postoperative adverse cardiac events, such as myocardial infarction (MI) or cardiac arrest [13]. According to the latest ACC/AHA recommendation, if the risk of reinfarction is high for at least 2 months after an MI,

coronary artery bypass grafting (CABG) but not percutaneous coronary intervention (PCI) may decrease that risk [12]. If patients require revascularization, elective surgery needs to be postponed, with the dilemma of how long to wait, as in the case of cancer where there is potential disease progression [14].

Cardiac stents, especially drug eluting ones, represent a significant problem due to the prolonged need for anticoagulation. Stopping dual antiplatelet therapy (i.e. aspirin and clopidogrel) is associated with a high risk of stent thrombosis, while continuing it leads to an increased risk of intra- and postoperative bleeding precluding regional anesthetic techniques [15]. The duration of the anticoagulation is usually based upon the type of stent: bare metal stents commonly require 4–6 weeks while in the presence of drug eluting stents 12 months are recommended for elective procedures, and 6 months for urgent cases [12]. The risk of stent thrombosis is higher for drug eluting stents, especially if the stent is long, at a bifurcation, if the revascularization is incomplete, or the patient has history of diabetes or heart failure [15]. A non-randomized observational prospective study done in non-cardiac surgery patients who had cardiac stents placed within a year from surgery, found a 44.7% rate of postoperative cardiac complications and a 4.7% mortality rate [16]. Dual antiplatelet therapy was stopped on average 3 days prior to surgery and substituted with intravenous unfractionated heparin or subcutaneous enoxaparin. Most of the complications occurred within the first 35 days from the stent placement and were cardiac in nature. Bleeding was not a significant variable. This data was not confirmed by another small prospective observational study done in 16 patients undergoing major lung resection 4 weeks after coronary angioplasty or PCI [17]. Dual antiplatelet therapy was given for 4 weeks and interrupted 5 days prior to surgery when it was bridged with low molecular weight heparin. No MI or deaths were reported. Despite the absence of randomization, these studies stress several important points. Once the antiplatelet treatment is stopped, low molecular weight heparin should be used (heparin alone is insufficient). All non-life-saving procedures should be postponed at least for 6–12 weeks from the stent placement, and aspirin should be continued up to the day of surgery [18, 19]. The protective effects against MACE in the immediate postoperative period outweigh the lower risk of postoperative bleeding [18]. Prophylactic revascularization (CABG versus PCI) does not seem to add further benefits over optimal medical treatment in patients with cardiac risk undergoing elective major vascular surgery [12, 14]. Long term survival as well as myocardial infarction, death and hospital length of stay seems to be unchanged. However, CABG is associated with less postoperative myocardial infarctions and decreased hospital length of stay when compared to PCI, probably because of better revascularization [20]. According to the ACC, revascularization should be reserved for patients with unstable angina or advanced coronary artery disease [12]. If revascularization is needed before surgery, bare metal stents or balloon angioplasty are the preferred options due to their lower risk of thrombosis [19]. In both cases, elective surgery needs to be appropriately delayed to prevent graft or stent thrombosis.

Patients with a history of COPD, prior lung resection, chronic lung disease or morbid obesity should undergo *pulmonary function testing (PFTs)* in anticipation of one-lung ventilation (OLV). A computed tomography (CT) scan or positron emission tomography (PET) scan of the chest done for cancer staging or to assess chemotherapeutic treatment response may also be used by the anesthesiologist to evaluate airway abnormalities or lung disease. Poor PFTs are associated with an increased incidence of respiratory complications, with potential benefits from preoperative pulmonary rehabilitation or training (i.e. incentive spirometry, deep diaphragmatic breathing, coughing). Respiratory rehabilitation has been proposed as part of a multidisciplinary approach to improve respiratory mechanics and decrease complications [21].

Preoperative staging may involve endoscopic ultrasound *(EUS) evaluation*, which is done as an outpatient procedure and requires an anesthetic [22]. The decision between sedation versus general anesthesia is based on the severity of symptoms and the experience of the provider.

Patient Selection

Predicting which patients are going to have a complicated recovery or mortality following esophagectomy is valuable information for all involved. In general, poor overall health and pre-existing organ system dysfunction negatively impact esophagectomy outcomes [23].

The use of *scoring algorithms* can add objectivity to the selection criteria.

1. The *Glasgow Prognostic Score* (GPS) combines elevated C-Reactive protein and hypoalbuminemia as markers of systemic inflammation. Seven studies of the GPS and modified GPS (mGPS) in esophageal cancer have shown prognostic value independent of tumor stage and pathological features [24].
2. The Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity (*POSSUM*), Portsmouth *(P) POSSUM* and upper gastrointestinal *(O) POSSUM* models were developed for calculating risk-adjusted mortality using a two-part scoring system: a 12-factor physiological score and a six-factor operative severity score. A comparison of the three models showed that P-POSSUM provided the most accurate prediction of in-hospital mortality after esophagectomy [25]. A comparison of POSSUM models with mGPS showed that the POSSUM physiology score was useful in predicting postoperative morbidity, while the mGPS was the best predictor of cancer-specific survival [26].

Cardiopulmonary exercise testing (CPET) is a method for determining a patient's physiological capacity to tolerate the stress of surgery. The test involves exercising against increasing levels of known resistance in the form of a cycle ergometer, treadmill or a hand crank for approximately 10 min while recording ventilatory parameters, inspiratory and expiratory gases, blood pressure, and electrocardiogram. From this data, the body's maximum oxygen uptake and the anaerobic threshold (the point at which anaerobic metabolism exceeds aerobic metabolism) are determined [27]. In elderly patients undergoing major abdominal or thoracic surgery, results of CPET have shown that an anaerobic threshold of <11 ml/kg/min predicted postoperative cardiopulmonary deaths [28]. While a dynamic predictor of a patient's preoperative exercise capacity such as CPET would be useful for esophagectomy patients, it has yet to be proven to correlate well with postoperative cardiopulmonary morbidity with adequate discriminatory ability in this population [29, 30].

In sum, risk stratification based on scoring systems and exercise testing alone should not be used to exclude patients from surgery. Data from these evaluations when added to clinical experience serves to guide discussion and decision-making when there is concern for high-risk patients.

Optimization

Reduction of modifiable risk factors is the main focus in preparation for surgery, with an emphasis on smoking cessation, correction of anemia, and improved metabolic state.

1. In a retrospective analysis, the incidence of pneumonia decreased with a longer duration of *smoking cessation* prior to esophagectomy. It is unclear how long is needed to decrease postoperative complications, with some providers suggesting at least 4–8 weeks [31]. Another study showed smoking cessation ≤30 days was an independent risk factor for pneumonia and smoking cessation ≤90 days was an independent risk factor for other severe morbidities [32]. It is strongly recommended that the perioperative provider counsel patients at the preoperative visit and may suggest behavioral and pharmacological interventions [3]. Respiratory physiotherapy has been studied (i.e. inspiratory muscle training) and shown to improve respiratory function but not incidence of postoperative pneumonia after esophagectomy [33].
2. *Anemia* is commonly found with esophageal cancer and increases the likelihood of red blood cell transfusion, which is significantly

associated with higher overall complications and increased risk of surgical site infections [34]. Iron deficiency anemia may be corrected preoperatively with oral or intravenous iron supplementation; oral iron takes 2 weeks to increase the serum hemoglobin level and 2 months to normalize it [35]. Intravenous iron infusions may correct anemia faster. It is unclear if the use of iron supplements with or without erythropoietin decrease the need for transfusion [36].

3. *Malnutrition* is likely to predispose to postoperative complications and is exacerbated by surgical stress and metabolic demands of recovery. While nutrition is not easily improved in patients with dysphagia, a nutritional assessment should be performed and attempts to improve nutrient intake should be made. *Carbohydrate loading* prior to appropriate preoperative fasting may attenuate the surgical stress response, insulin resistance and subsequent hyperglycemia, as well as muscle breakdown of the patient [37, 38]. In severe cases of malnutrition, feeding tubes can be placed prior to surgery. However, elective enteral nutrition has not been shown to improve outcome prior to neoadjuvant treatment and therefore should not be recommended unless deemed necessary [39].

Intraoperative Management

Surgical Approach

The anesthetic preparation must consider the planned surgical approach, as each has its own considerations. Independent of the technique (open versus minimally invasive) and the type of operation (Ivor Lewis, McKeown, transhiatal), patients undergoing esophagectomy are at risk of aspiration on induction and emergence and require optimal analgesia. Invasive monitoring is commonly used independently of the technique, due to the potential arrhythmias during the dissection or in the postoperative period. Proper positioning to avoid neuropathy is essential for cases of long duration [40]. *Extubation* at the end of the case is recommended to avoid ventilation associated respiratory failure and hemodynamic instability as a consequence of the sedation required to tolerate the ventilator.

Open approaches involving large incisions and violating both the peritoneal and pleural cavities makes it a painful procedure for the patient. Inadequate pain control can complicate extubation and impair effective pulmonary toilet and ambulation during recovery without a multimodal analgesic plan in place. Proper analgesia is important, usually in the form of epidural or paravertebral catheters, removed within 2–3 days if the patient is enrolled in an enhanced recovery after surgery (ERAS) pathway.

Minimally invasive esophagectomy (MIE) has become more popular since the early 2000s, particularly at high-volume academic centers, with the goal of decreasing risk and improving outcomes by decreasing surgical stress, inducing less postoperative pain, and easing recovery overall. All forms of dissections can be performed minimally invasively [40], with similar morbidity and mortality to the open approach [41–43]. The main concern for these cases is related to the position, the creation of pneumoperitoneum and pneumothorax, and arrhythmias during the thoracic phase. In most cases, patients are first in reverse Trendelenburg followed by lateral decubitus. However, the prone position is used in some centers for the thoracoscopic dissection [44]. Steep reverse Trendelenburg requires that the patient is secured to prevent falls and that the feet are padded. Hypotension can occur soon after positioning and abdominal insufflation due to a decreased venous return and may require intravascular volume loading and/or vasopressor or inotrope administration. At the time of the crural dissection, pneumothorax may develop and require desufflation of the peritoneal cavity, fluid and vasopressor/inotrope administration, leveling of the operating room table, and decompression of the pleural cavity with chest tube placement in severe cases [45].

Intraoperative Monitoring

The duration and complexity of esophagectomy require the ability to monitor patient hemodynamics and metabolic state comprehensively and expeditiously. Standard monitoring should include pulse oximetry, noninvasive blood pressure monitoring, electrocardiography, and temperature monitoring. Placement of an **arterial line** for continuous blood pressure monitoring is commonly used to guide hemodynamic support and ventilator settings, especially for OLV. Furthermore, surgical dissection in the thorax and manipulation of the mediastinum has the potential for large vessel compression or injury and stimulation of cardiac dysrhythmias that need to be detected and intervened upon quickly. Arterial blood samples from the arterial line may be used for point-of-care analysis of hemoglobin level, electrolyte balance, acid-base status, arterial oxygenation and lactic acid concentration. **Central venous access** is usually unnecessary except in cases of difficult intravenous access or vasopressor infusion. If a cervical approach is being employed, left internal or external jugular venous cannulation should be avoided and implanted ports in the left chest wall should not be used. A temperature probe can be placed in the oropharynx, nasopharynx, external auditory canal, bladder, or rectum. However, care should be taken to avoid placement of temperature probes or other devices in the esophagus except in conjunction with the surgical team.

Induction and Airway Management

Induction of anesthesia for esophagectomy should be done with comorbid conditions and particularly aspiration pneumonitis risk in mind. While some patients may be able to swallow normally with minimal or no GERD, or have complete resolution of dysphagia after neoadjuvant chemotherapy, anesthesiologists must be vigilant for this risk and take precautions when appropriate. The head-of-bed should be kept elevated at 30° until the airway is secured. A rapid sequence induction is advocated using an intravenous induction agent, such as propofol, and succinylcholine or rocuronium for rapid-onset neuromuscular blockade. A double lumen tube (DLT) or single lumen tube (SLT) with bronchial blocker may be used to provide OLV during transthoracic procedures, especially for minimally invasive techniques [46]. Fiberoptic bronchoscopy confirms correct placement of either device and reassessment should be performed after patient position changes. If the surgical team is planning an initial flexible bronchoscopy for evaluation of airway involvement or if the patient has disadvantageous anatomy, a SLT may be placed and subsequently exchanged for a DLT or kept in place for use with a bronchial blocker. Attempting a rapid sequence induction for placement of a DLT can be challenging even for experienced providers and should be approached thoughtfully and with a plan in case of difficult intubation. Videolaryngoscopy or fiberoptic bronchoscopy can greatly improve glottic view for easier DLT placement and can be part of the primary or backup plan [47]. A supraglottic airway device may be placed for rescue of failed intubation, though it is not ideal for patients at risk for aspiration. Once in place, it may be exchanged for an endotracheal tube. Finally, awake intubation may be necessary for patients who have an anticipated difficult airway.

Ventilator Management

Protective lung strategies have been advocated intraoperatively due to the potential for lung injury that can be more pronounced after OLV. Postoperative pulmonary complications remain the most common type of complication after esophagectomy, with a prevalence of 20–40% according to National Surgical Quality Improvement Program (NSQIP) data [48]. Perioperative acute lung injury is multifactorial, resulting from surgical trauma, alveolar inflammation, and ventilator-induced lung injury (VILI). Protective strategies include maintaining low tidal volumes based on predicted body weight, optimizing positive end expiratory pressure (PEEP), performing routine recruitment

maneuvers, reducing inspired oxygen concentration, avoiding high peak inspiratory and plateau airway pressures, and limiting the duration of OLV [49, 50]. Precise guidelines for ventilation parameters are yet to be elucidated.

Analgesia

Effective pain control for esophagectomy can have widespread benefits for the patient, and it is an important component of many enhanced recovery pathways. *Thoracic epidural analgesia* (TEA) remains the gold standard for open esophagectomy, reducing the systemic inflammatory response and providing better pain relief than parenteral opioids [51, 52]. Epidural catheters are usually placed preoperatively at a thoracic level that allow coverage from T4 to L1. Commonly used medications include a diluted local anesthetic with or without opioid—typically bupivacaine or ropivacaine with fentanyl or hydromorphone. There is some evidence that preemptive analgesia with TEA reduces acute postoperative pain for thoracotomy when compared to TEA initiated at completion of surgery [53], but there are no studies dedicated to esophagectomy and the sympathectomy-related hypotension may be counterproductive. In addition to effective pain control, demonstrated benefits of TEA include facilitation of early extubation, better analgesia for postoperative mobility, and reduced incidence of pneumonia and anastomotic leak [52, 54]. TEA can have complications, such as urinary retention, hypotension, and failed or incomplete block [54]. *Paravertebral block* (PVB) or catheters are an alternative to TEA, providing equivalent analgesia with fewer pulmonary complications and more favorable overall side effect profile when used for thoracotomy [55]. PVB is a more challenging procedure than epidural placement, as it requires injection or catheter placement in a deep space. With the advent of the ultrasound guidance the success rate has improved but still requires more practice than with epidural placement. Paravertebral catheter can be placed intraoperatively under direct vision by the surgeon before chest closure. The main advantage for PVB is its unilaterality, the main disadvantage is the lack of coverage for the abdominal incision. To date, there are no prospective studies that have compared PVB vs TEA for thoracolaparotomy or esophagectomy.

Peripheral nerve blocks are used when neuraxial techniques are contraindicated. Extrapleural intercostal nerve blocks and transversus abdominis plane blocks are viable opioid-sparing regional techniques. Early reports show the serratus plane block and erector spinae plane block may also be effective for thoracotomy pain with low-risk profiles [56, 57]. Even so, peripheral nerve blocks provide suboptimal analgesia alone; opioids and adjuvants are still needed. Various intravenous and oral medications may be added to the analgesic regimen, such as acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), alpha-2 agonists (e.g. clonidine or dexmedetomidine), NMDA antagonists (e.g. ketamine or magnesium), and gabapentinoids (gabapentin and pregabalin). Studies specific to the efficacy of these analgesic adjuvants for esophagectomy are lacking. Of note, concern has risen with the use of NSAIDs for colorectal surgery because of an association with impaired anastomotic healing and increased rate of leakage, and their use in esophagectomy patients may be unfavorable [58, 59]. Gabapentin has been associated with sedation and respiratory depression after laparoscopic surgery especially in the elderly patients and when combined with long acting opioids and benzodiazepines [60].

Currently, there is no gold standard analgesic for MIE. Unlike for open esophagectomy, use of TEA for minimally invasive procedures is variable and mostly dependent on patient respiratory comorbidities. Multiple port sites and fields of operation still cause enough pain that multimodal analgesia is required for patient comfort and recovery. If not contraindicated for the patient, a thoracic epidural should be placed preoperatively for MIE if there is a likelihood of conversion to an open procedure. Patients with chronic opioid use and tolerance, history of side effects or allergy to opioids, poor respiratory function, propensity for delirium, or other conditions that make opioid use less effective or desirable will also likely benefit from TEA for MIE.

Fluid Management

There is still lack of evidence on the appropriate amount of fluids needed during esophagectomy. As for any other surgery, fluid management should target euvolemia, homeostasis and normal physiology [36]. The volume and the type of fluid used should be customized to the patient and the type of surgery [61]. Fluid restriction to the point of hypovolemia could decrease cardiac output and tissue oxygen delivery, compromising renal function and perfusion of the esophagogastric anastomosis. Conversely, liberal fluid administration to the point of excess could cause shifts into the interstitial space, impairing anastomotic healing and bowel function and contributing to pulmonary complications [62]. The type of fluid administered is as important as the volume used. Balanced crystalloids are recommended, especially for short procedures, while for major surgery, colloids are added to balanced-salt solutions [36]. There is no current evidence that the use of colloids or gelatins increases morbidity and mortality in various type of shocks. Moreover, outcome data from prolonged use of colloids may not be applicable to the surgical population, which is exposed for limited time intervals. Extrapolating from existing studies on fluid administration and complication rates after thoracic surgery and esophagectomy, suggested total intraoperative fluid volume is between 3 ml/kg/h and 10 ml/kg/h [63], but emphasis should be made that individual fluid requirements vary widely and there is no data on the role of fixed fluid replacement on outcome. A more objective approach on guiding fluid replacement is based on *goal directed fluid therapy* (GDFT), which measures surrogates of fluid requirements, such as stroke volume, cardiac output, and fluid responsiveness, to individualize the needs in a dynamic setting. The challenge for using GDFT in esophagectomy is that flow-related hemodynamic endpoints may be inaccurate with an open hemithorax or in the presence of pneumoperitoneum like in case of MIE. The data is also affected by the presence of arrhythmias, mechanical ventilation with low tidal volumes (<8 cc/kg IBW), and decreased chest wall compliance. Both esophageal Doppler and transesophageal echocardiography are not applicable in esophagectomy, making the use of GDFT techniques overall difficult to apply. A decrease in the incidence of pneumonia has been observed in the GDFT arm of an observational quality improvement project where GDFT with a noninvasive cardiac output monitor was compared to standard treatment in patients undergoing either MIE or open esophagectomy [64].

NPO status guidelines have changed, especially with the advent of ERAS pathways, allowing patients to have clears up until 2 h preoperatively. Thus, preoperative intravascular volume depletion is minimal (200–400 cc) with no need for replacement. Bowel preparation is also not used routinely, contributing to less preoperative volume deficit [61].

Perfusion of the Esophagogastric Anastomosis

Anastomotic leak due to ischemia of the esophagogastric anastomosis is a devastating complication after esophagectomy. Preservation of perfusion of the gastric conduit for adequate tissue oxygenation of the anastomotic site is key. Blood supply to the gastric fundus, which is used to construct the conduit, is reduced in the process of ligating arteries for gastric mobilization. Thus, blood flow to the anastomosis is heavily reliant on the local microvascular network within the greater curvature and fundus of the stomach. For the anesthesiologist, avoidance of hypotension is important for perfusion, though supranormal mean arterial pressures do not improve gastric conduit perfusion in experimental models [65]. Hypotension due to anesthesia or TEA can be readily corrected with vasopressor or inotrope administration [66]. The belief that vasopressors should be completely avoided during esophagectomy is unfounded and is not supported by the literature. A study using laser speckle contrast imaging to intraoperatively assess microcirculation 1 mm below the tissue surface showed that

changes in perfusion were related more to the operative procedure than to TEA-use or phenylephrine support [67]. ERAS pathways have used norepinephrine or dopamine as weak inotropes to support blood pressure if necessary with no adverse effects on the esophageal anastomosis [64]. New modalities are needed to ensure healing of the esophagogastric anastomosis and some promise has been shown with intraoperative use of indocyanine green fluorescein imaging to forewarn of areas of poor perfusion [68].

Postoperative Recovery

Complications

Adverse outcomes can occur postoperatively in up to 60% of esophagectomy patients [69].

Pulmonary complications are the most common, and primarily include pneumonia, aspiration pneumonitis, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), bronchopleural fistula, atelectasis, and pulmonary embolism. ARDS is the most critical pulmonary complication with mortality rates up to 50% [70]. There are a multitude of factors that contribute to these adverse pulmonary outcomes [71]. Intraoperative mechanical ventilation may be a significant component especially when combined with surgical manipulation and lung isolation. Poor analgesia or excessive sedation can lead to poor respiratory efforts, contributing to hypoventilation. Opioid-related sedation can also contribute to aspiration.

Cardiovascular complications also account for significant morbidity and mortality after esophagectomy, predominantly in the form of arrhythmias. Supraventricular tachyarrhythmias, mostly atrial fibrillation, occur in about 18% of cases [72] and lead to a higher rate of ICU admission, longer hospital stay and higher 30-day mortality rate [73]. Several protocols are in place for the treatment, mainly relying on pharmacological cardioversion (amiodarone, sotalol) or rate control with beta blockers, calcium channel blockers, or amiodarone. Age, gender, type of procedure and elevated BNP (>30 pg/ml) have been associated with an increased postoperative risk of developing atrial fibrillation [74]. Amiodarone or calcium channel blockers are the drugs of choice for prophylaxis. Beta-blockers should be continued in patients already taking them. Magnesium, statins, and ACE inhibitors have also been proposed as weak prophylactic agents.

Esophageal anastomotic leakage adds to the morbidity of recovery and significantly increases the mortality in the postoperative period. Other less common but notable complications include chylothorax, recurrent laryngeal nerve injury, ileus, abscess formation and wound infection. These are complications that may require surgical treatment and therefore the need of an anesthetic.

Enhanced Recovery Pathway

Formalizing results from well-conducted, peer-reviewed studies into a streamlined protocol of perioperative care known as an enhanced recovery after surgery (ERAS) pathway has been successful in minimizing complications and speeding recovery for a variety of surgical populations [36]. This approach is now being evaluated for its effectiveness in esophagectomy care, given that a comprehensive set of interventions is likely needed to see an overall improvement in outcomes. The general focus of an ERAS pathway is on five categories of care: (1) preoperative assessment, planning, and preparation before admission; (2) reducing the physiologic stress of the operation; (3) a structured approach to immediate postoperative and perioperative management, including pain relief; (4) early mobilization; and (5) early enteral feeding [75].

Currently, there is minimal evidence for individual interventions for esophagectomy, with many recommendations derived from non-esophageal thoracoabdominal surgery. Yet, adapting existing ERAS protocols to esophagectomy is a logical approach and has promise to make surgical treatment of esophageal cancer safer for the patient.

Conclusions

With the advent of minimally invasive surgical techniques and the creation of ERAS pathways, an increased number of challenging patients will be considered candidates for resection. The role of the anesthesiologist will become more active in the coordination of care with other providers. Optimizing the functional status in the preoperative period, planning each aspect of the anesthetic, and preventing medical complications in the postoperative period are all goals for a successful operation. This will require a group effort from several specialists involved in each stage of the perioperative period.

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Transhiatal Esophagectomy

9

Francisco Schlottmann and Marco G. Patti

Introduction

Transhiatal esophagectomy (THE) with a cervical anastomosis is an established procedure for the treatment of esophageal cancer. It is important to select the proper patients for this procedure, mostly avoiding patients with severe mediastinal adhesions secondary to prior operations or radiotherapy, or those with a T4 tumor. Cancers of the distal esophagus are well suited for this procedure, as most of the dissection of the area involved by the cancer can be done under direct vision. The theoretical advantages of the THE include avoidance of respiratory complications as a thoracotomy is not performed, and avoidance of mediastinitis in case an anastomotic leak occurs because a leak at the cervical level is mostly a local problem. The oncologic properties of the THE have been questioned because, contrary to a transthoracic esophagectomy (TTE), it does not allow dissection of lymph nodes in the posterior mediastinum. However, retrospective and prospective studies, as well as meta-analyses have shown no difference in survival when the THE has been compared to a TTE, suggesting that the key determinant of survival is not the type of operation chosen, but rather the staging of the disease at the time the operation is performed and the biological behavior of the cancer.

The technique of the THE, and the prevention and treatment of the most common complications are the focus of this chapter.

Surgical Technique

Patients are admitted the morning of surgery. A thoracic epidural catheter is inserted in the preoperative area. Heparin, 5000 units subcutaneously, and intravenous antibiotics are given before induction, and pneumatic compression is applied to the lower extremities. A single lumen endotracheal tube and a nasogastric tube are inserted. A radial artery catheter is essential for monitoring of the blood pressure, particularly during the blunt mediastinal dissection. The patient is placed supine on the operating room table with a blanket between the shoulders. The arms are secured at the side of the table, and the patient's head is turned slightly towards the right. The operating field extends from the left ear to the pubis, and laterally all the way to the posterior axillary line so that chest tubes can be inserted if the pleural cavities are entered during the mediastinal dissection.

F. Schlottmann
Department of Surgery, Hospital Alemán of Buenos Aires, University of Buenos Aires, Buenos Aires, Argentina

M. G. Patti (✉)
Department of Medicine, University of North Carolina, Chapel Hill, NC, USA

Department of Surgery, University of North Carolina, Chapel Hill, NC, USA
e-mail: marco_patti@med.unc.edu

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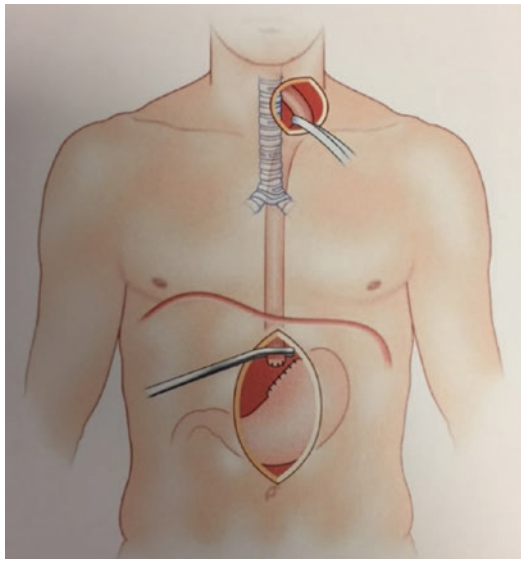

Fig. 9.1 Transhiatal esophagectomy. Reproduced with permission from Atlas of Esophageal Surgery, P. Marco Fisichella, Marco G. Patti editors, Springer

The THE has three components: abdominal, mediastinal and cervical (Fig. 9.1).

Abdominal Component

The abdominal cavity is entered through a midline incision extending from the xiphoid process to the umbilicus. A self-retained retractor is used, particularly to lift the right and left costal margins and provide exposure to the sub-diaphragmatic area. The abdomen is inspected carefully to rule out metastases in the liver, carcinomatosis or ascites.

The left triangular ligament is incised in order to retract the left lateral segment of the liver towards the right and expose the gastro-hepatic ligament and the esophageal hiatus. The gastro-hepatic ligament is incised all the way to the right pillar of the crus. The right gastric artery is preserved. The phreno-esophageal membrane overlying the esophagus is divided. If an aberrant left hepatic artery originating from the left gastric artery is found, it is transected in between silk ligatures. A window is opened between the right pillar of the crus and the esophagus, and the posterior mediastinum is entered. Gentle dissection will determine if the tumor can be freed from the surrounding structures.

After identification of the right gastroepiploic artery, the gastro-colic omentum is opened initially towards the pylorus and then along the greater curvature. The short gastric vessels are then divided all the way to the left pillar of the crus. During this phase of the dissection it is of paramount importance to avoid injury to the spleen. This problem is usually caused by traction exerted in order to provide exposure, particularly to the upper short gastric vessels. It can be minimized by using a long 5 mm laparoscopic bipolar instrument to coagulate and divide these vessels, avoiding the use of ligatures. If a small splenic capsule tear occurs, use of the cautery and gentle packing will frequently stop the bleeding. Dissection is then continued between the esophagus and the left pillar of the crus, and a Penrose drain is passed around the esophagus. Particularly when dealing with distal esophageal tumors or tumors of the esophago-gastric junction, it is possible to determine under direct vision if the tumor is mobile and can be separated from the surrounding structures. After this determination is made, the coronary vein, the left gastric artery and the surrounding nodal tissue are dissected. The vessels are transected at their base with an Endo-GIA stapler with a vascular cartridge. Posterior gastric adhesions are divided.

The duodenum is mobilized with a Kocher maneuver. Adhesions with the gallbladder and the porta hepatis are divided. A pyloroplasty is then performed by opening the pylorus longitudinally and the closing it transversally with interrupted 3-0 silk sutures. We do prefer this technique rather than a pyloromyotomy, as it guarantees division of all the muscular fibers and avoids concerns of leaving small holes in the mucosa. Alternatively, botulinum toxin can be injected in the pylorus, a technique that is frequently used when the preparation of the stomach is done laparoscopically.

A loop of jejunum 30–40 cm distal to the ligament of Treitz is chosen for the placement of a feeding jejunostomy. A Weitzel tunnel is created with interrupted 3-0 silk sutures, and the jejunal loop is then fixed to the abdominal wall.

Cervical Component

A 6 cm incision is made along the anterior border of the left sternocleidomastoid muscle (Fig. 9.2). The platysma is divided, the omohyoid muscle is exposed and divided. The carotid sheath is retracted laterally, and the prevertebral fascia is exposed by blunt dissection. The inferior thyroid artery is ligated: the recurrent laryngeal nerve is usually visible just deep and medial to this vessel. The trachea and the larynx are gently retracted medially with a finger as metal retractors should not be used to avoid injuring the nerve (Figs. 9.3 and 9.4). The esophagus is then encircled with a right angle clamp and a narrow Penrose drain is passed around the esophagus (Fig. 9.5).

Mediastinal Component

A good part of the mediastinal dissection can be performed under direct vision. This is facilitated by the division of 1 or 2 cm of the rim of the esophageal hiatus anterior to the esophagus, in between sutures. The anterior and posterior vagus nerves are divided. Most of the dissection can be performed with the same bipolar instrument used for the division of the gastro-colic omentum and the short gastric vessels, usually reaching all the way to the carina. The remaining mediastinal dissection is done blindly, and some rules must be followed to avoid damage to mediastinal structures. It is important to have a large nasogastric tube inside the esophagus and keep the dissecting hand always in contact with it. Initially, the posterior plane is developed along the prevertebral fascia, separating the esophagus from the spine. Then the anterior plane is developed with the surgeon's hand turned down so that the palm is in contact with the anterior aspect of the esophagus (Fig. 9.6). This maneuver displaces the airway anteriorly. At this point, the esophagus is quite mobile, and the lateral attachments of the middle and upper esophagus can be easily divided, reaching the dissection started in the neck. The blind mediastinal dissection is the most delicate and risky portion of the THE. It is important to be aware of the following potential complications:

- *Hypotension*. This is caused by the mechanical compression of the surgeon's hand. It can be prevented by having good filling pressures before the dissection is started, and is usually treated by simply withdrawing the hand, allowing the blood pressure to normalize.

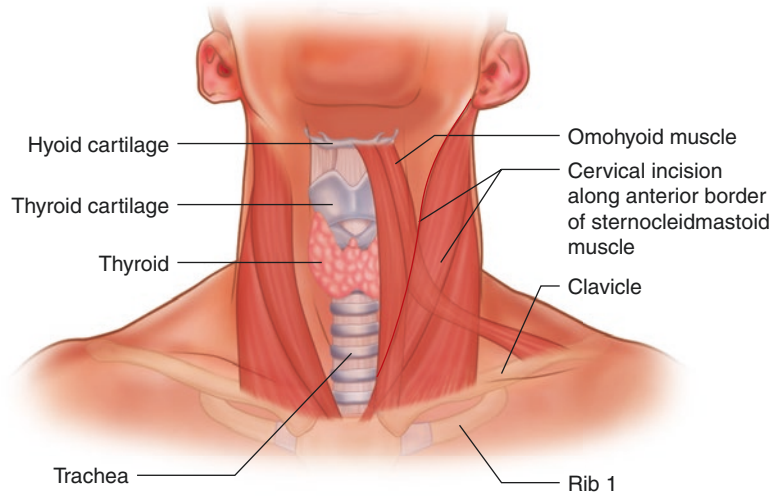

Fig. 9.2 Cervical incision

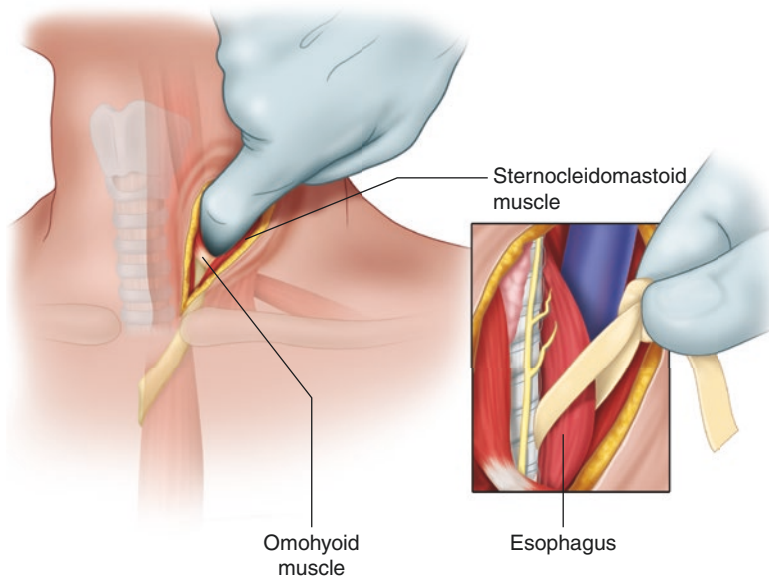

Fig. 9.3 The tracheoesophageal groove and recurrent nerve are constantly protected with the surgeon's finger, and a Penrose drain is used to encircle the esophagus

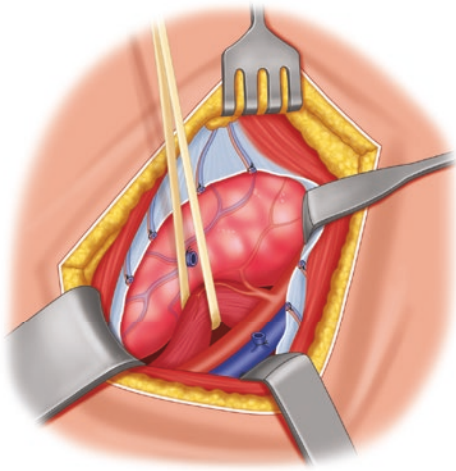

Fig. 9.4 The middle thyroid vein and inferior thyroid artery divided

- *Cardiac arrhythmias*. Usually self-limited, and caused by the irritation of the pericardium.
- *Violation of one or both pleural spaces*. If it occurs, it requires placement of chest tubes.
- *Bleeding*. It is key to keep the dissecting hand in continuous contact with the esophagus so that the feeding blood vessels are transected when they enter the esophageal wall and then contract. Massive bleeding is usually secondary to a torn azygos vein. The mediastinum should be immediately packed tightly and a thoracotomy performed to control the bleeding.
- *Tracheal laceration*. Lacerations of the membranous portion of the trachea are quite rare. They manifest with loss of large volumes of the insufflated gas and inadequate patient's ventilation. In these cases, the single lumen endotracheal tube should be advanced into the left mainstem bronchus to prevent significant loss of insufflated tidal volume. Tears just above the carina are best repaired through a right thoracotomy. Higher tears can be approached through the cervical incision or require a partial sternal split.

The conduit is then prepared using multiple fires of an endo-GIA, in order to create a gastric tube whose blood supply is based on the right gastric artery and on the right gastroepiploic artery. The esophagus is transected in the neck, a wide Penrose drain is attached to the distal esophagus so that when the esophagus is delivered through the abdominal incision, the Penrose is now below the diaphragm. The drain is then attached with interrupted sutures to the tip of the gastric fundus and using a combination of pushing and gentle pulling, the gastric conduit is delivered into the neck incision. The stomach

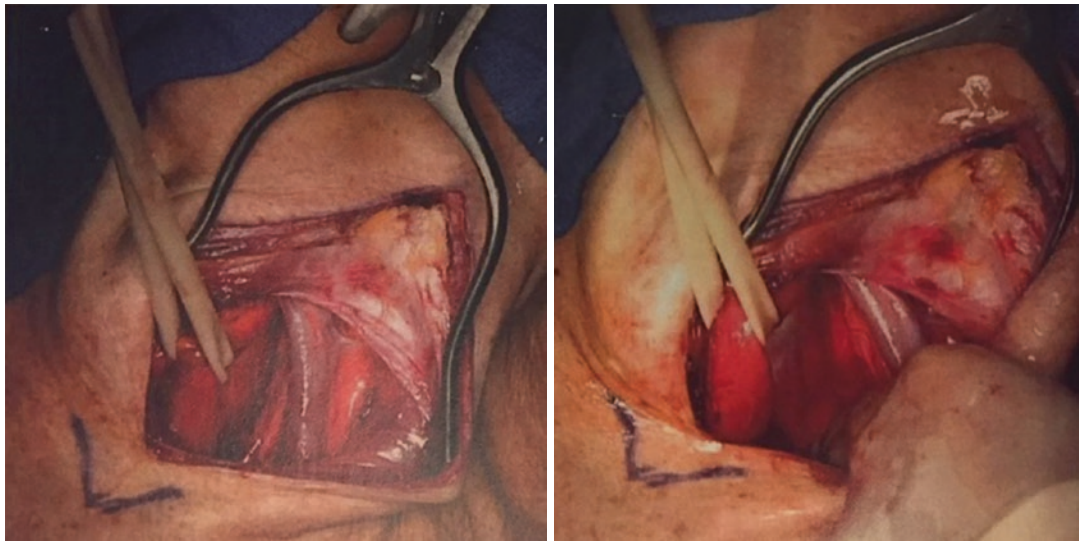

Fig. 9.5 Left cervical exposure. Vessel loop encircling the cervical esophagus with retraction of the sternocleidomastoid muscle, carotid artery, and internal jugular vein laterally, and the trachea and thyroid medially. Reproduced with permission from Atlas of Esophageal Surgery, P. Marco Fisichella, Marco G. Patti editors, Springer

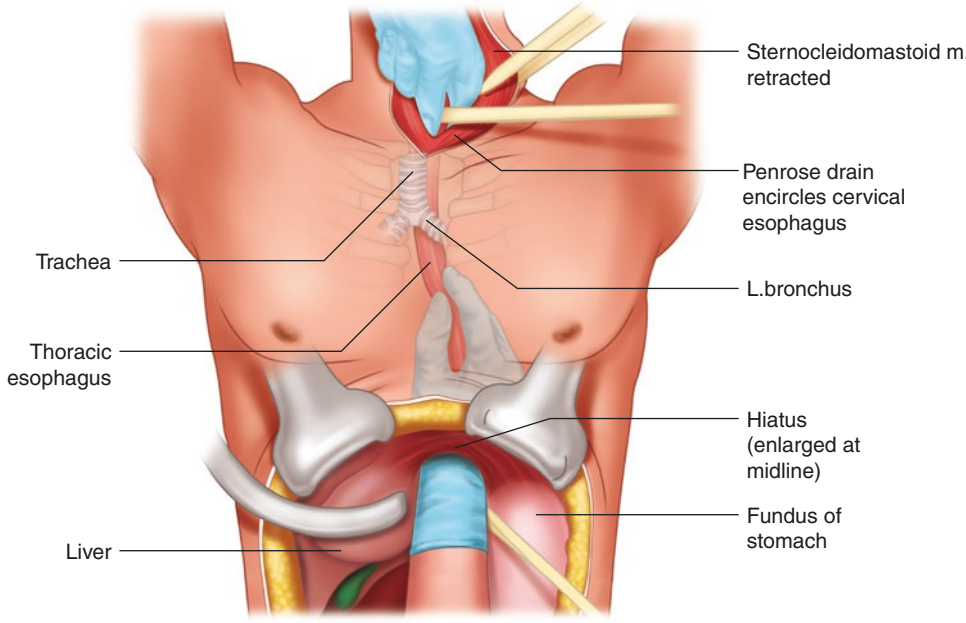

Fig. 9.6 Transhiatal dissection of the esophagus

must be oriented so that the greater curvature is toward the patient's left. The esophageal hiatus is then narrowed with interrupted sutures in order to avoid herniation of viscera such as the colon. However, compression of the gastric vessels must be avoided.

Anastomosis

If 4–5 cm of the gastric conduit lay above the left clavicle without tension, we prefer to perform a side-to-side, semi-stapled anastomosis. The transected esophagus is placed over the anterior wall of the stomach and stay sutures are placed between the anterior wall of the stomach and the right and left side of the esophagus. Additional 4-0 silk sutures are placed anteriorly and laterally including all the esophageal layers in order to avoiding proximal sliding of the mucosa. A 2 cm gastrotomy is then made next to the cut edge of the esophagus, and a 30 mm Endo-GIA stapler with a vascular cartridge is inserted, with one arm in the stomach and one in the esophagus. The nasogastric tube is pulled back all the way to the oro-pharynx. By firing the stapling device, an anastomosis is made between the posterior wall of the esophagus and the anterior wall of the stomach. The staple line is inspected for bleeding, and minor oozing can be stopped using the cautery. The nasogastric tube is then advanced down the esophagus into the stomach. The anterior opening is closed in two layers, an inner layer of running 3-0 absorbable suture (the running layer is done using two sutures, starting at the right and left corner. The two sutures are tied in the middle), and an outer layer of interrupted 3-0 silk sero-muscular Lembert sutures. If the side-to-side anastomosis would be under tension, it is preferable to perform a hand sutured end-to-end anastomosis, using an inner layer of running absorbable 3-0 sutures, and an outer layer of interrupted 3-0 silk Lembert sutures.

Before closing the cervical incision in layers, a # 10 Jackson-Pratt drain (exteriorized lateral to the upper portion of the incision) is placed next to the anastomosis and in the upper mediastinum. Because of its suction action, this type of drain is more effective than a Penrose drain in case of a leak because the Penrose would not prevent the leakage to reach the mediastinum when the patient is in the upright position.

The abdominal incision is then closed and the operation is completed. A chest X-ray is obtained while the patient is intubated and if a pneumothorax is detected a chest tube is inserted. Extubation is done if all the respiratory and hemo-dynamic parameters are satisfactory. It is better to leave the patient intubated rather than have an emergent endotracheal re-intubation, which would require extension of the neck.

Postoperative Course

We usually remove the nasogastric tube on day 3, and obtain a barium swallow on day 5. If no leak is detected a liquid diet is initiated and then advanced to a soft mechanical diet as tolerated. When it is felt that the patient is not taking enough calories by mouth, tube feedings cycled at night can be used to supplement the caloric intake.

Suggested Readings

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Ivor Lewis Esophagectomy

10

Nassrene Y. Elmadhun and Manjit S. Bains

Introduction

Resection of esophageal carcinoma is a relatively complex operation that has evolved greatly in the last 100 years. The first successful esophagectomy for cancer was described by Franz Torek in 1913 through a left chest approach. The patient survived with an esophagostomy and gastrostomy for 12 years [1]. Esophagectomy with intrathoracic reconstitution of esophagogastric continuity was later described by Japanese surgeon Ohsawa in 1933 and by Adams and Phemister in 1938, and popularized by Sweet in 1942 with his descriptions of left sided approach to trans-thoracic esophagectomy [2, 3]. Though Sweet's approach to esophagectomy provided an important foundation for modern esophageal surgery, the left-sided approach for esophagectomy is particularly challenging, especially the blind dissection of the esophagus behind the aortic arch. The Welsh surgeon Ivor Lewis proposed an alternative right-sided approach for dissection and resection of the thoracic esophagus in 1946, which did not require a diaphragmatic incision, and would allow for dissection of the thoracic esophagus under direct visualization [4]. The Ivor Lewis technique became the preferred approach for proximal and mid-esophageal carcinomas reserving the left sided Sweet approach for distal esophageal tumors.

Ivor Lewis described his esophagectomy as a two-stage procedure. The first stage involved a midline laparotomy and mobilization of the stomach. The esophagectomy with esophagogastric anastomosis was performed through a right thoracotomy about a week later. It soon evolved into the one-stage procedure that remains the gold standard.

Indications

Common indications for Ivor Lewis esophagectomy include middle to distal esophageal carcinoma, esophageal motility disorders requiring resection of most of the esophagus, and distal tumors arising in a long segment of Barrett's esophagus. The Ivor Lewis approach allows for direct visualization of the thoracic esophagus and access to perform a complete thoracic lymphadenectomy.

Contraindications

For tumors located in the upper third of the esophagus, this technique does not provide adequate tumor free margin, and therefore these

N. Y. Elmadhun · M. S. Bains (✉)
Thoracic Surgery Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA
e-mail: elmadhun@mskcc.org; Bainsm@mskcc.org

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patients should be considered for total esophagectomy with a cervical anastomosis. Relative contraindications include previous thoracotomy, fused pleural space, and poor lung function.

Endoscopic Evaluation

Endoscopy should be performed by the surgeon at the time of the planned esophagectomy. The purpose is to determine the proximal and distal extent of the tumor. Tumors arising in the setting of Barrett's esophagus need to have the tumor resected with a 5-cm margin, and include the entire segment of Barrett's mucosa. Assessment of the degree of involvement of the stomach is crucial and may require retroflexion of the esophagogastroduodenoscope. Endoscopy also allows for clearing any residual enteric contents remaining in the stomach.

The carina is at 25 cm from the incisors. Patients with a tumor near the airway in the thoracic esophagus should be evaluated with a bronchoscopy to rule out invasion of the trachea, carina or main bronchi.

Surgical Technique

Abdominal Phase

With the patient placed in supine position, an upper midline abdominal incision is made for abdominal exploration to rule out metastatic disease such as peritoneal implants or liver metastasis, and to detect any invasion of tumor into adjacent structures. The limited upper midline incision is extended from the umbilicus to the sternum. The xiphoid process is split to maximize exposure. A self-retaining retractor is placed such as the Goligher, Buchwalter or Omni retractor. The left lobe of the liver is retracted cephalad with a self-retaining retractor. The gastrohepatic ligament is incised up to the right crus. The hiatus and distal esophagus are dissected anteriorly and posteriorly from the right side using blunt dissection or energy source. The abdominal esophagus is encircled and a Penrose drain is placed around the esophagus to assist in providing traction for dissection of the distal esophagus into the mediastinum. Dissection includes all tissues between pericardium anteriorly, the aorta adventitia posteriorly, and pleural reflections on either side. It is important to accomplish as much of the hiatal dissection of the lower esophagus from the abdominal side as possible, as it is more difficult to perform the dissection at the hiatus from a high right thoracotomy.

The gastrocolic ligament is incised to enter the lesser sac, taking care not to injure the right gastroepiploic arcade. Dissection along the greater curvature continues towards the spleen using an energy device such as the harmonic scalpel or Ligasure (Fig. 10.1). The short gastric vessels are divided close to the spleen and taken to the left crus.

A rim of omentum is left along the greater curvature to be used later to wrap the anastomosis and serve as a buttress between the gastric conduit and airway in the chest. The posterior aspect of the stomach is mobilized and adhesions, if present, between the stomach and pancreas are divided. The traditional Kocher maneuver can be performed to further mobilize the duodenum from its retroperitoneal attachments. Mobilization

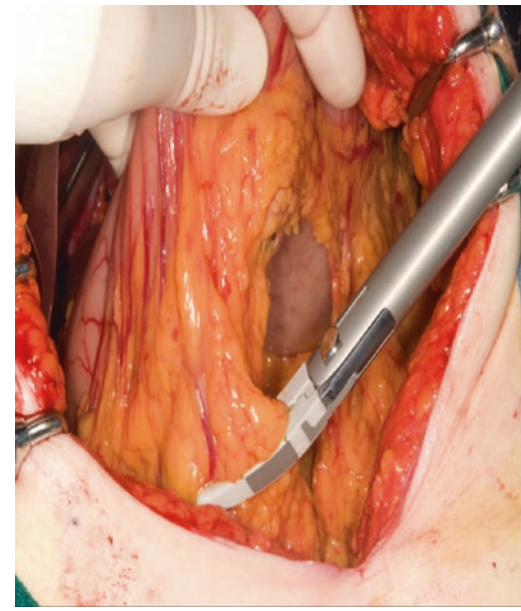

Fig. 10.1 Mobilization of the greater curvature of the stomach along the transverse colon

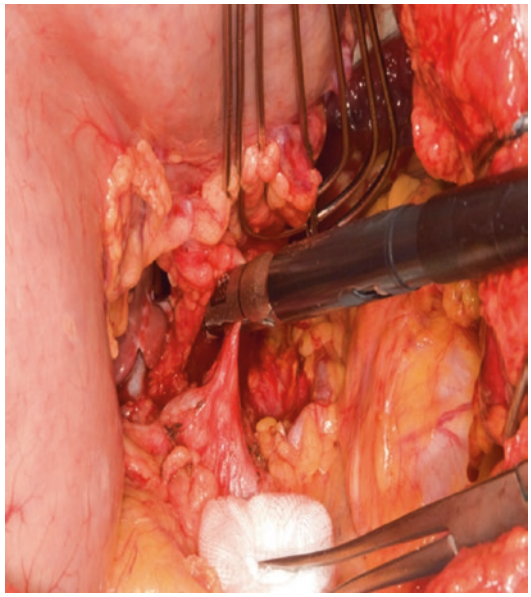

Fig. 10.2 The left gastric artery has been skeletonized and is being divided with a stapler. Also, the fatty and lymphatic tissues overlying the esophageal crura superior to the pancreas and the splenic artery have been dissected along with the specimen

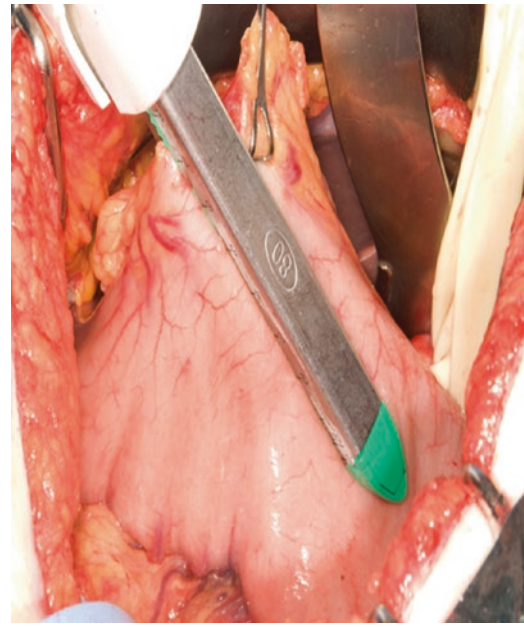

Fig. 10.3 Creation of the gastric conduit with linear stapler maintaining adequate margin from the tumor

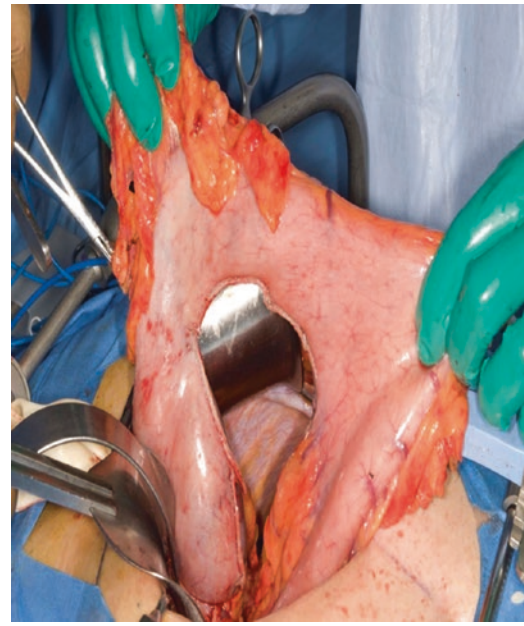

Fig. 10.4 The gastric tube has been constructed but the specimen is still attached to the gastric tube most proximally

is adequate when the pylorus can reach the right crus without tension. The left gastric artery is skeletonized by sweeping all nodal tissue to the specimen side and divided with a vascular stapler (Fig. 10.2).

Tailoring of the gastric conduit will depend on the extent of involvement of the stomach by the tumor. Ideally, the stomach is tubularized along the greater curvature maintaining a width of 4–5 cm (Fig. 10.3). Some surgeons believe that if the gastric tube is narrower, it improves emptying of the stomach. Normally, one can preserve the right gastric artery. However, if necessary to obtain additional margin, one can safely sacrificed the right gastric artery. Transection of the stomach along the lesser curvature usually starts at the junction of the proximal two third with the distal one third of the stomach. Grossly, one needs to maintain a margin of approximately 5 cm from the tumor. The most proximal part of the stomach is not transected allowing the gastric tube to be pulled up into the chest (Fig. 10.4). Transection of the stomach is completed in the chest. The staple line may be reinforced with interrupted Lembert sutures.

At the surgeon's discretion, a pyloroplasty, pyloromyotomy or Botox injection can be performed to facilitate gastric emptying. A meta-analysis of nine trials and 553 esophagectomy patients randomized to pyloromyotomy versus none found that patients who had a pyloromyotomy had a lower risk of gastric outlet obstruction (OR 0.18, 0.03–0.97, $p < 0.046$) and there was no difference in operative mortality, leaks, or pulmonary complications [5]. Although more recent studies have challenged the role of pyloroplasty or pyloromyotomy, larger prospective studies are required [6].

A feeding jejunostomy is inserted typically 40 cm distal to the ligament of Treitz. We routinely place a feeding jejunostomy tube to serve as definitive enteric access postoperatively until the patient is tolerating an oral diet. At that point, the jejunostomy tube can be discontinued. The abdomen is closed and the patient is prepared for the thoracic phase.

Thoracic Phase

The patient is re-positioned in the left lateral decubitus position with the right side up in preparation for a right thoracotomy. Single-lung ventilation will improve the exposure to the posterior mediastinum. A posterolateral right thoracotomy is performed sparing the serratus muscle. The chest is entered in the fourth or fifth interspace. The lung is retracted anteriorly and the inferior pulmonary ligament is divided. The pleura posterior to the esophagus is incised along the pericardium to the carina. The subcarinal lymph nodes are cleared from the right and left mainstem bronchi. The azygous vein is circumferentially divided with a vascular stapler. The vagus nerve is identified at this level and divided to avoid traction injury to the recurrent laryngeal nerve. The pleural incision anterior to the esophagus is carried down from the azygous vein to the hiatus. All periesophageal fatty and nodal tissue is swept towards the specimen side. The esophagus is dissected circumferentially from the vertebral body to the pericardium. Care should be taken to carefully clip or tie any lymphatics that are encountered to avoid possible chylothorax. Arterial branches originating from the aorta are also clipped or tied. The esophageal dissection is carried up towards the apex of the chest to obtain an adequate margin, which is usually 5–7 cm. The nasogastric tube is pulled back to avoid incorporating it inadvertently in the anastomosis.

Anastomosis

Though we prefer the EEA stapled circular anastomosis, several anastomotic techniques have been described including hand sewn (single layer vs double layer), stapled (circular vs side to side linear stapled anastomosis), and hybrid techniques [7–10]. Studies have not definitively proven one technique to be superior over another technique. In a meta-analysis evaluating 12 randomized control trials with over 1400 patients, there was no difference in the incidence of anastomotic leak (RR 1.02, 95% CI 0.66–1.59) or postoperative mortality (RR 1.64, 95% CI 0.95–2.83) [10] in circular stapled anastomosis compared to the hand sewn technique. There was an increased incidence of anastomotic stricture (RR 1.67, 95% CI 1.16–2.42) and decreased operative time for the circular stapled anastomosis compared to the hand sewn anastomosis.

Surgeon preference and experience is the most important determinant for choosing the technique for fashioning the esophagogastric anastomosis. For the stapled *EEA anastomosis*, we start by placing an auto purse-string clamp on the proximal esophagus and the esophagus is divided sharply (Fig. 10.5). The anvil is inserted in the esophagus and the purse-string is securely tied around the anvil (Fig. 10.6). The stomach is then pulled into the chest, making sure that the conduit is not twisted in the process. A gastrotomy is created in the part of the stomach that will be resected to insert the EEA stapler. The site of anastomosis is selected based on vascularity of the conduit, orientation of the conduit, and the distance away from the linear staple line. Any tension or redundancy of the stomach must be avoided. One can inspect the anastomosis from

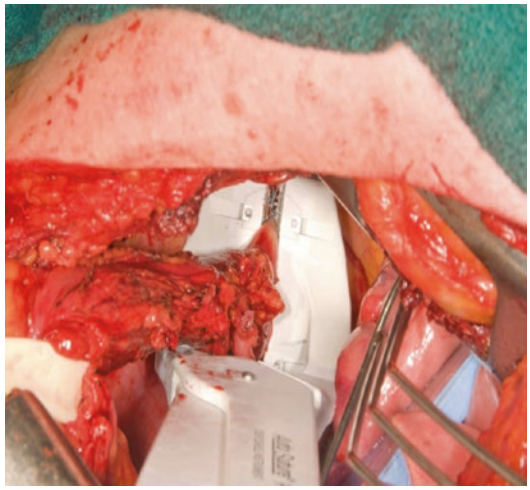

Fig. 10.5 A purse-string is being applied at the site selected for the anastomosis using a purse-string applicator

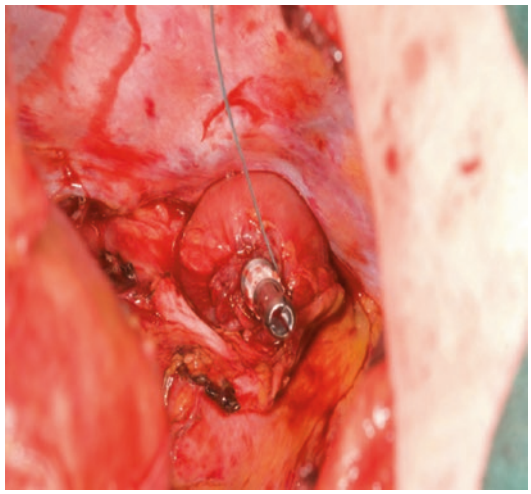

Fig. 10.6 The anvil of the circular EEA has been placed in the lumen of the esophagus and the purse-string has been tied

inside by looking through the gastrostomy for insertion of the EEA staples and while doing that, advance the nasogastric tube under direct vision. A stapler is used to divide the excess stomach and finalize the conduit. The specimen is submitted to pathology for frozen section of resection margins. The staple line may be reinforced with sutures for seromuscular approximation, burying the staple line.

The *linear stapled anastomosis* is performed by making a 1.5 cm gastrostomy in the stomach at least 2 cm away from the stapled edge of the stomach. A single silk stitch is placed to align the open end of the esophagus to the stomach. One end of a linear stapler is placed in the stomach and the other limb of the stapler is placed in the esophagus. The stapler is then closed and fired creating a common channel between the esophagus and gastric conduit. The stapler is removed and the nasogastric tube is advanced past the anastomosis under direct visualization. The remaining anterior hole in the esophagus/gastric conduit can be closed in two hand sewn layers or with an additional linear stapler [7–10].

The traditional *two-layered hand sewn anastomosis* involves scoring a 2 cm circle on the surface of the stomach at least 2 cm away from the staple edge to avoid leaving an ischemic strip of devascularized stomach. Two corner stitches are placed on each end and a row of interrupted silk sutures are placed between the esophagus and stomach. This row of silk stitches will serve as the back row of the anastomosis. The gastric bite should include the seromuscular layer and the esophageal bite should include the longitudinal and circular muscle layers of the esophagus. The esophagus is opened sharply from one corner stitch to the other corner stitch. The scored 2 cm mark on the stomach is also sharply incised and removed. The inner layer is completed circumferentially with mucosal bites on the esophagus side and full thickness bites on the gastric side of the anastomosis. Prior to placing the last stitch, the nasogastric tube is advanced under direct visualization past the anastomosis. The outer row is completed with interrupted silk stitches.

After the anastomosis is completed, the remaining omentum is used to wrap around the conduit and tucked between the staple line and the airway to prevent possible fistula. Any redundant stomach is reduced back into the abdomen and the conduit is sutured to the diaphragmatic hiatus to prevent paraconduit hernia. The conduit is also secured to the mediastinal pleura to take some of the tension off the anastomosis. Chest tubes are placed anteriorly and posteriorly and the thoracotomy incision is closed, and the

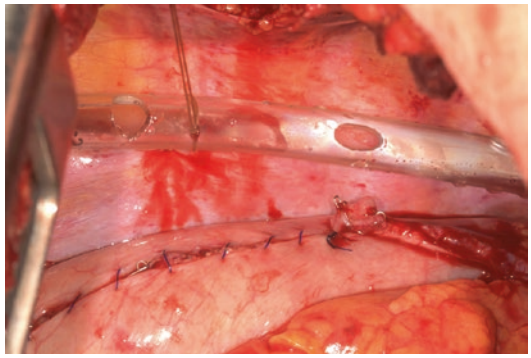

Fig. 10.7 A chest tube is placed parallel to and about 1 cm from the gastric tube. This tube can be useful in overriding any collection of fluid in case of anastomotic leak

posterior chest tube or a JP drain is placed approximately 1 cm removed from the stomach, parallel to the stomach (Fig. 10.7).

Complications

Ivor Lewis esophagectomy is a morbid procedure; complications can be reduced by paying meticulous attention to details [11–13]. In one of the largest series of 228 patients undergoing open Ivor Lewis esophagectomy, 10% had significant complications including 7% with cardiovascular complications, 4% with leaks, 3% required reoperation for bleeding, 1% with chyle leak and 2% 30-day mortality [14].

Anastomotic Leaks

Anastomotic leak typically presents within the first week with signs of evolving sepsis and high chest tube output with drainage that is turbid or bilious in character. Evaluation with esophagram or a CT with water-soluble contrast can reveal the location and size of the leak, intrapleural contamination, and undrained collection in the pleura. A well-drained leak may resolve with conservative management, antibiotics, and bowel rest. Endoscopic placement of a covered stent can also be used to seal the leak and expedite healing [15, 16]. In septic patients with large leaks, percutaneous drainage of any intrapleural collection and antibiotics should be tried first. If these measures do not work, operative exploration including debridement, drainage, decortication, and even diversion may become necessary.

Anastomotic Stricture

Benign stricture can occur in the weeks to months following Ivor Lewis esophagectomy as a result of ischemia, leak or use of a small diameter circular stapler [17, 18]. Treatment involves endoscopic and/or contrast imaging evaluation to rule out recurrent disease, and dilation either with a tapered or balloon dilator. Patients frequently need more than one treatment in order to manage the anastomotic stricture. Some patients will learn and tolerate self-dilation. Alternatively, retrievable self-expanding esophageal stents can be placed temporarily for the management of anastomotic stricture [19].

Chylothorax

Chylothorax presents as unusually high chest tube output that may be serous or milky in character. The diagnosis can be confirmed by checking the triglyceride level in the fluid after a fat challenge. Low output chylothorax (defined as daily output less than 1 liter in 24 h) can be managed conservatively with bowel rest and total parenteral nutrition. If the output persists, or if the chylothorax is high output (defined as daily output greater than 1 liter in 24 h) then intervention such as lymphangiogram and thoracic duct embolization can be performed by interventional radiology. Alternatively, the thoracic duct can be ligated surgically either by a transthoracic or transabdominal approach [20].

Conduit Ischemia

Conduit ischemia occurs as a result of compromise of the conduit blood supply and manifests as early clinical deterioration typically within the

first 2–3 days of surgery. Initially, patients may present with tachycardia, arrhythmia, or an increased oxygen requirement. Since conduit ischemia can progress rapidly with sepsis, it is important to have a low threshold for performing esophagoscopy to evaluate for gross ischemia. In the setting of gross ischemia and hemodynamic instability, reoperation is indicated with take-down of the conduit, cervical esophagostomy, wide drainage and staged reconstruction at a later date [21].

Conclusions

Open Ivor Lewis esophagectomy has withstood the test of time for the resection of mid to distal esophageal carcinoma. Proper preoperative patient selection and meticulous attention to operative technique can lend the best chance to achieving an R0 resection and minimize the chances of postoperative complications.

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McKeown Esophagectomy

11

Ian Wong and Simon Law

Introduction

For squamous cell carcinoma, the majority of intrathoracic esophageal carcinomas are located at the middle and lower esophagus. For adenocarcinoma, 75% are located at distal esophagus or around the gastroesophageal junction. Two-phase esophagectomy with laparotomy and right thoracotomy was first described independently by Lewis and Tanner in 1946 and 1947 respectively. McKeown, in 1976, described a three-phase esophagectomy which began with the abdominal approach, followed by right thoracotomy and cervical phase. Three-phase esophagectomy has its advocates. It provides maximal proximal margin from the primary tumor. When superior mediastinal lymph node dissection is performed (especially indicated for squamous cell cancers), it makes sense to perform the anastomosis in the neck since the upper esophagus has been mobilized. Although leak rates are generally reported to be higher for a cervical anastomosis as compared to an intrathoracic anastomosis, it is easier to manage as drainage via the neck wound is generally effective. When a neck anastomosis is chosen, the conduit for esophageal replacement can be brought up via the posterior mediastinal, retrosternal as well as subcutaneous route. The ability to choose different routes are important, e.g. when colonic interposition is required, or in cases of palliative resection or when postoperative radiotherapy to the mediastinum is planned, the retrosternal route is often preferred. In this chapter, the important points in surgical technique, available adjuncts, and tips on intraoperative trouble-shooting are described.

I. Wong · S. Law (✉)
Division of Esophageal and Upper Gastrointestinal Surgery, Department of Surgery, The University of Hong Kong, Queen Mary Hospital, Hong Kong, China
e-mail: slaw@hku.hk

Surgical Technique

The McKeown operation (three-phase esophagectomy) involves thoracic esophageal mobilization and lymphadenectomy; abdominal exploration, gastric mobilization and lymphadenectomy; and cervical incision for anastomosis. Modifications of the initial publication in 1976 are many, depending on: (1) The approach: open, video-assisted thoracoscopic (VATS), laparoscopic, hybrid or robotics; (2) The sequence: the initial Mc Keown operation started with abdominal phase, followed by thoracic and right cervical incision. Most centers now start with thoracic phase followed by abdominal and cervical phase in a supine position and the patient would only need to change position once. (3) The construction of gastric conduit: The original approach used the whole stomach. A narrower gastric tube

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of around 3–4 cm in diameter is more commonly utilized; the conduit is lengthened and there is also less chance of delayed gastric emptying. (4) The technique of anastomosis: different centers favor different methods in terms of suture material, number of layers of sutures, and use of linear or circular stapler. Regardless of the modification, the fundamental steps of the operation include the abdominal, thoracic and the cervical phase which are described in detail below.

Thoracic Phase

The authors perform the procedure through a right thoracotomy in the left lateral decubitus position. A single-lumen endotracheal tube with right bronchial blocker is preferred over a double lumen tube for one-lung ventilation. A single lumen tube is less traumatic and stiff, and allows easier retraction of the trachea and left main bronchus during superior mediastinal lymphadenectomy. However, the blocker is often displaced by retraction and needs close cooperation and communication with the anaesthetist. If superior mediastinal dissection is not planned, a double-lumen tube ensures more certain lung collapse.

An anterolateral thoracotomy is usually made at the fifth intercostal space. Depending on the site of tumour, extent of (superior mediastinal) lymphadenectomy and the anatomy of the patient, the fourth space can be chosen for the thoracotomy. A controlled fracture of the posterior fifth or sixth rib is made, after careful dissection to avoid injury of the intercostal pedicle. Bleeding at the bony cut end is controlled with bone wax. The intercostal space can be further enlarged by gradual retraction using two rib spreaders, placed diagonally to each other. Sometimes extensive adhesions are encountered, and may be time-consuming to free.

Starting at the lower esophagus, the inferior pulmonary ligament is divided. The dissection plane proceeds along the posterior surface of the pericardium, superiorly towards the root of inferior pulmonary vein and posteriorly towards the left side of the pleura. In case of locally advanced tumour, the left side pleura and part of the pericardium can be resected en-bloc. A separate incision is made at the mediastinal pleura posterior to the esophagus, joining the dissection plane anteriorly behind the pericardium, to encircle the lower esophagus. The lower esophagus can now be slung with a suture for retraction. The mediastinal pleura incision is continued inferiorly to circumscribe the hiatus, exposing both crura and removing the supradiaphragmatic lymph nodes en-bloc. The thoracic duct is identified close to the hiatus by isolating the tissue between the azygos vein and the surface of the aorta. The duct is ligated to prevent chylothorax and is marked with metal clip as a radiological guide in case of leakage. The incision at the posterior mediastinal pleura is continued proximally along the azygos vein until the arch of azygos is reached. The arch of azygos vein is isolated and divided between ligature or transfixion. The right bronchial artery beneath the azygos vein can be sacrificed. Lymphadenectomy is performed by removing the tissue on the surface of the aorta together with the thoracic duct. Anteriorly, along the plane of the posterior pericardium, the dissection should reach the right main bronchus and the tracheal bifurcation. Careful lymphadenectomy is performed at the subcarina and bilateral bronchi. Bleeding may be encountered but is usually self-limiting and can be controlled by gauze packing. Sharp or thermal injury to the airway should be prevented. This concludes the dissection of the middle and lower esophagus. In case of bulky tumour with difficult retraction, the lower end of the thoracic esophagus can be divided with a stapler and the stump can be retracted cranially to aid exposure.

In the superior mediastinum, the plane between the trachea and esophagus is entered posterior to the right vagus nerve. Posteriorly, the pleura opening is extended from inferiorly at the arch of the azygos vein up to the apex superiorly. The aortic arch is exposed and the esophagus is dissected away from the spine and left side pleura. Another suture can be used to sling the esophagus. The superior mediastinal and recurrent laryngeal nerve lymphadenectomy is essential for squamous cell cancers. The pleura on the tracheoesophageal groove is incised along the

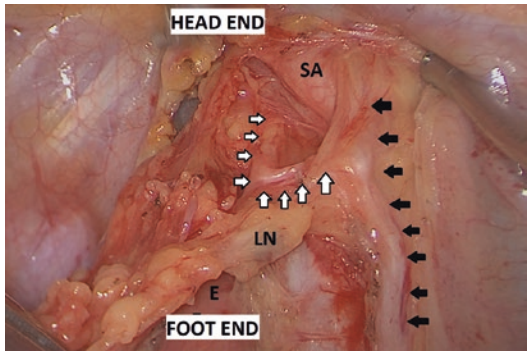

Fig. 11.1 Right recurrent laryngeal nerve lymphadenectomy. *SA* Subclavian artery, *E* esophagus, *LN* lymph node. Black arrow: right vagus nerve. White arrow: right recurrent laryngeal nerve

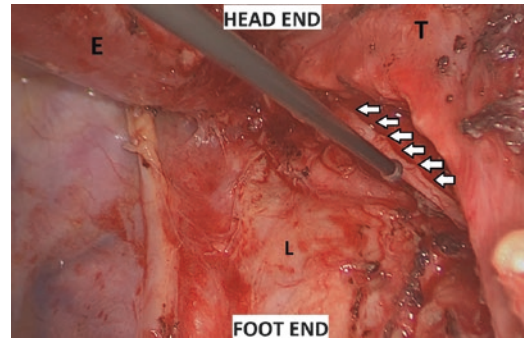

Fig. 11.2 Left recurrent laryngeal nerve lymphadenectomy. *E* Esophagus (retracted posteriorly), *T* Trachea (retracted anteriorly), *L* Left lung. White arrow: left recurrent laryngeal nerve (after lymphadenectomy). The integrity of the left recurrent laryngeal nerve is checked by the ball-tip intermittent nerve stimulator

right vagus nerve and then on the surface of the right subclavian artery. With blunt dissection, the right recurrent laryngeal nerve should be found as a thin glistering white structure branching off from the right vagus nerve, travelling posteroinferior to the right subclavian artery within the fatty tissue. The location and integrity of the nerve can be checked by nerve stimulator. Sizable lymph nodes are often found next to the right recurrent nerve (Fig. 11.1). These lymph nodes are contiguous with the cervical chain of paratracheal and para-esophageal lymph nodes. Dissection around the nerve has to be carefully performed, avoiding excessive heat energy from instruments such as diathermy and ultrasonic energy sources.

The esophagus is dissected away from the membranous part of the trachea until the left side of the cartilaginous trachea C-ring is reached. The trachea is rotated and retracted anteriorly and the esophagus is pulled posteriorly by the sling to expose the left tracheoesophageal groove. With blunt dissection, the left recurrent laryngeal nerve should be identified along the left side of the trachea. The sympathetic nerve runs in parallel to and sometimes mimics the left recurrent laryngeal nerve. The integrity and location of the nerve can be checked by nerve stimulator (Fig. 11.2). Extra care should be taken in subaortic lymph node dissection to prevent injury to the pulmonary artery, which is potentially lethal. The whole thoracic esophageal dissection is now completed. A Fr 24 chest drain is inserted towards the apex. The authors prefer a Fr 19 round fluted drain connected to vacuum drainage. This is much more comfortable and allows easy ambulation. A formal chest tube is only inserted when extensive adhesiolysis has been performed since air leak is more efficiently drained by a conventional chest tube with underwater seal. After confirming lungs expansion, ribs are approximated with suture. Muscle and skin are closed in layers.

Abdominal Phase

Patient is placed in a supine and reversed Trendelenburg position. Upper midline or a bilateral subcostal incision is usually used. The authors prefer the bilateral subcostal incision as it gives excellent exposure to the upper abdomen, hiatus and the left subphrenic region, which may be difficult especially in obese patients. The spleen is brought forward by placing a piece of gauze posteriorly to prevent traction injury. The mobilization of stomach begins by dividing the gastrocolic ligament away from the right gastroepiploic arcade. Care is taken during manipulation and retraction of the stomach to prevent injury to the arcade. Once the lesser sac is reached, dissection can be continued towards the

direction of the spleen. Complete omentectomy is not needed. Large pieces of omentum will make the conduit bulky and make delivery of the stomach to the neck difficult. The anastomosis between left and right gastroepiploic vessels is often incomplete. The pancreatic tail acts as a landmark for the origin of the left gastroepiploic vessels, where they should be divided. Short gastric vessels should be ligated or divided with energy source. One should be cautious to prevent injury to the spleen. Small lacerations of the spleen can be controlled by simple packing or haemostatic agents. An easier way to prevent splenic injury is to dissect close to the gastric wall. The gastric fundus is rotated medially, after dividing the attachment to the diaphragm to expose the left crus. The dissection of the right side of the gastrocolic ligament continued until the right gastroepiploic origin is reached. Posterior adhesions between the stomach and the pancreatic capsule is divided until the gastroduodenal artery is visualized.

The gastrohepatic ligament is incised to expose the right crus, celiac trifurcation and supra-pancreatic region. Aberrant left hepatic artery, which originates from left gastric artery, is not uncommon. A sizable vessel, if sacrificed, can result in deranged liver function or even liver necrosis. It can be preserved by dissecting from the origin of the left gastric artery to remove any surrounding lymph nodes, and divide distally after branching off the aberrant left hepatic artery. For dissection of the celiac axis, the lesser curve of the stomach should be retracted anteriorly, and the pancreas should be retracted downwards. The dissection should begin at the superior border of the pancreas, to the right, along the anterior surface of the hepatic artery proper, limit by the hepatoduodenal ligament. Attention should be made to prevent injury to the right gastric artery which is branching off from the common hepatic artery. To the left, dissection is performed along the splenic artery which is often tortuous. The left gastric (coronary) vein is found draining either anteriorly to the splenic vein or posteriorly to the portal vein. It should be isolated and divided. A lot of lymphatic channels are running through this area, large lymphatics should be ligated, clipped or cauterized by energy source to prevent chyle leakage. With the upward retraction of the stomach, the left gastric artery should be clearly running vertically, and it should be divided at its origin. The lymphadenectomy is continued along the surface of the aorta towards the hiatus. With tedious dissection, the whole procedure can be a bloodless exercise. The phreno-esophageal ligament between the right crus and abdominal esophagus is divided, meeting the dissection plane on the left. The whole hiatus and abdominal esophagus should now be mobilized. For advanced lower esophageal tumour that have transmural involvement at this level, part of the crural muscle can be resected en-bloc. A sling, such as a cotton tape, Pen-rose drain or latex tube can be looped around the abdominal esophagus for better retraction. The mobilization of stomach is complete and is ready for gastric conduit creation after retrieval of the specimen.

Cervical Phase

The author opts for a left supraclavicular incision because the esophagus is more inclined to the left side at this level. The incision is extended medially from midline to just beyond the sternocleidomastoid muscle laterally. The strap muscles are divided with electrocautery, exposing the thyroid gland underneath. The thyroid and trachea are retracted to the right side, exposing the carotid sheath. The middle thyroid vein is now visible and should be divided to gain exposure. Along the dissection plane medial to the carotid sheath and prevertebral fascia posteriorly, signs of apical dissection at the thoracic phase should be evident. The esophagus can easily be slung by a finger or a cotton tape, where it is identified anterior to the spine and posterior to the trachea. One should be extra cautious with the recurrent laryngeal nerves as they are unprotected after extensive dissection at the thoracic phase (Fig. 11.3). The detail of cervical lymphadenectomy will not be discussed here. The cervical esophagus can now be divided at a desirable location with an adequate margin from the

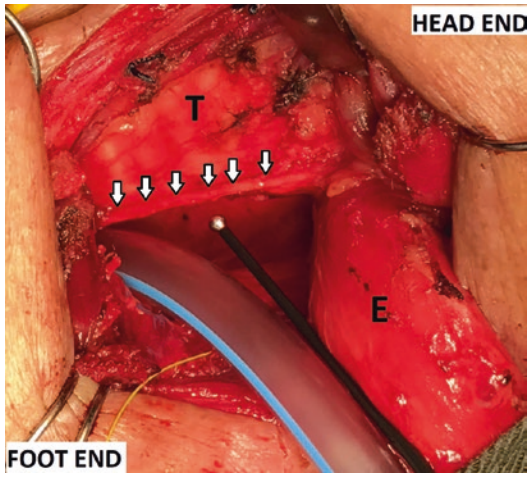

Fig. 11.3 Left recurrent laryngeal nerve after dissection at cervical phase. *T* Trachea, *E* proximal esophageal stump (transected and retracted cranially). White arrow: left recurrent laryngeal nerve tested by a ball-tip intermittent nerve stimulator. Chest drain is attached to the distal esophageal stump and delivered to the abdomen via the posterior mediastinal route

tumour. The proximal esophageal stump is opened and anchored at four directions with stay sutures. The distal stump is closed and tagged to a chest tube. The esophageal specimen together with the distal end of the chest tube is retrieved through the abdomen.

Creation of Gastric Conduit and Anastomosis

After delivering the esophageal specimen and the mobilized stomach outside the abdomen, the gastric conduit is created. On the lesser curvature, the right and left gastric arcade anastomosis is divided at a point distal to the third branch of the left gastric artery. This point is chosen for oncological reasons. It has been documented that the majority of lymph node metastases are found in proximity to the origin of the left gastric artery and the risk is relatively negligible distal to its third branch. The stomach is then straightened and gently stretched, and the highest point is marked at the fundus. The lesser curvature is transected with linear staplers from the arcade division point towards the tip of the fundus to create a narrow gastric tube (Figs. 11.4 and 11.5). A narrow gastric tube theoretically has better gastric emptying than a whole stomach. A Heineke-Mikulicz pyloroplasty is performed in two layers with continuous absorbable monofilament sutures to further enhance the drainage. Pyloromyotomy, as advocated by Mc Keown, is equally effective. The perfusion of the gastric conduit is checked, and the tip of the fundus is tagged to the distal end of the chest tube. The conduit is then delivered to the neck via the posterior mediastinal route inside a transparent plastic bag. One should pay extra attention to the axis of the lesser curve and the staple line to ensure that there is no rotation. After haemostasis, the abdomen is closed in layers without drainage.

Esophago-gastric anastomosis can be performed with handsewn technique, circular or linear staplers. Stricture rate tends to be higher when a small-sized circular stapler is used. There is no difference in leakage rate across different methods of anastomosis. The authors prefer handsewn anastomosis as it is more economical, less dependent on length and position of the conduit, and more controllable. The tip of the gastric fundus is opened up for anastomosis (Fig. 11.6). The anastomosis is performed in a single-layer continuous manner with a double needle monofilament absorbable sutures. It starts with the distal angle of the esophagus and stomach. The posterior layer is first completed in a continuous manner, across the proximal angle to the anterior wall at the proximal end. The other end of the needle is then used to complete the anterior layer from distally, incorporating and inverting the staple line (T-Junction) into the anastomosis until it reaches the suture at the proximal end. Before completion of the anastomosis, a Fr 16 nasogastric tube is inserted into the gastric lumen under direct vision. The two ends of the needle are tied, and the anastomosis is complete. A metal clip is applied near the knot for a radiological guide in case of postoperative leakage. A Fr 15 round fluted drain is inserted close to the anastomosis. The platysmas and skin are closed in layers.

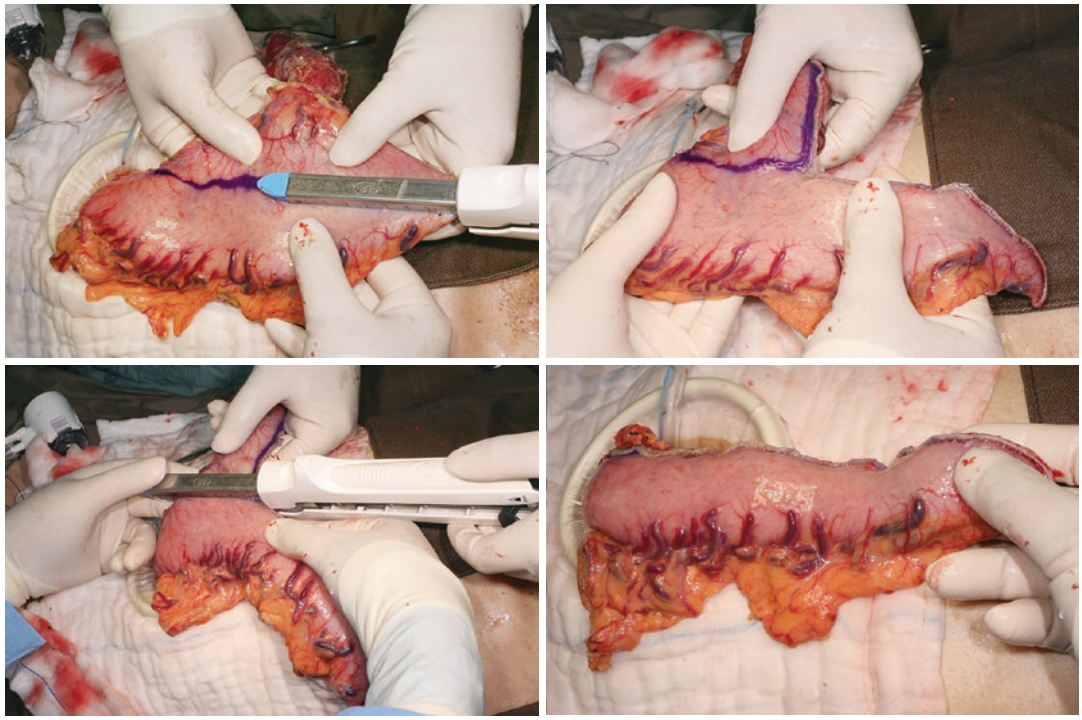

Fig. 11.4 Gastric conduit construction. Serial linear staplers are applied from the tip of the fundus along the predesigned path towards lesser curvature (the third branch distal to the origin of the left gastric artery). It would result in a narrow gastric tube of around 3–4 cm in width

Adjuncts, Pitfalls and Intraoperative Complications

For every surgical complication, prevention is better than cure. However, when intraoperative complications occur, one should react promptly and calmly.

Lung Parenchyma and Airway Injury

In patients with previous pulmonary insults, e.g. tuberculosis or other inflammatory conditions, extensive adhesiolysis is expected. Lung parenchymal injury may result in significant air leak, subsequent pneumothorax, and surgical emphysema postoperatively. One should actively check for such injury by communicating with the anaesthetist in terms of ventilator readings and search for any active bubbling under positive ventilation. Small injuries can be managed conservatively or by commercially available tissue glue or fibrin sealant patch. A formal chest drain should be inserted and put on low suction postoperatively. For refractory cases, chemical pleurodesis may be needed. For large defect or significant airway injury, thoracic surgeons should be consulted for repair or even covered stent insertion.

Aortic or Major Vascular Injury

During lymphadenectomy along the surface of the aorta, we usually work on an avascular plane. However, in advanced tumour or a tumour with previous neoadjuvant therapy, desmoplastic or fibrotic changes may occur and make the dissection plane less well-defined. Thinning of the aortic adventitia or tearing of small intercostal or bronchial branches from the aorta may cause torrential bleeding. One should remain calm

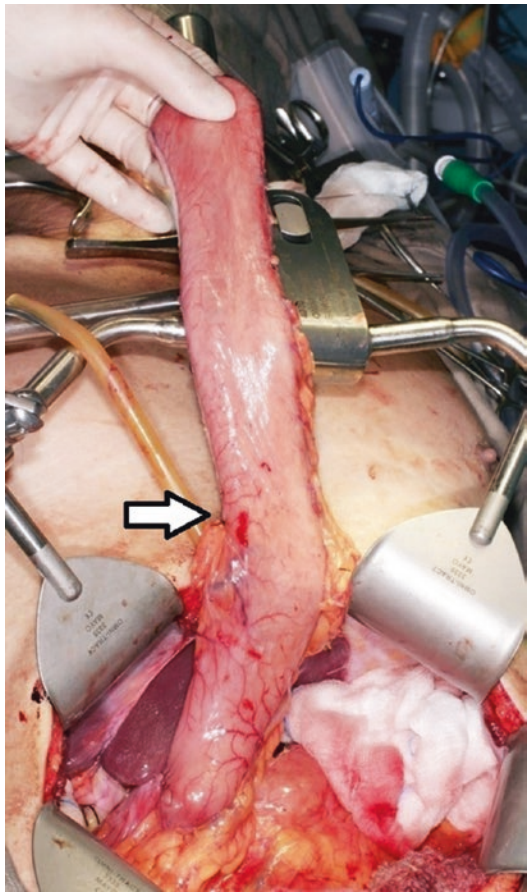

Fig. 11.5 Gastric conduit construction. White arrow: Division of the lesser curvature arcade at the third branch distal to the origin of the left gastric artery. Linear staplers can also be applied from this point towards the tip of the fundus. Adequate length of the conduit is checked by bringing up the tip of the conduit extracorporeally, which should be able to reach the neck without tension

as the defect is usually small and can be temporarily controlled with digital compression. Communication with the anaesthetist is important for potential heavy blood loss and the need for blood product replacement. After confirming the anatomy and site of injury, smaller defects can be repaired by pledged sutures. Tight control of blood pressure intraoperative and postoperatively is important. For larger defect, cardiac surgeons should be consulted for repair under cardiopulmonary bypass. Staged procedure with delay reconstruction should be considered if the patient is unstable.

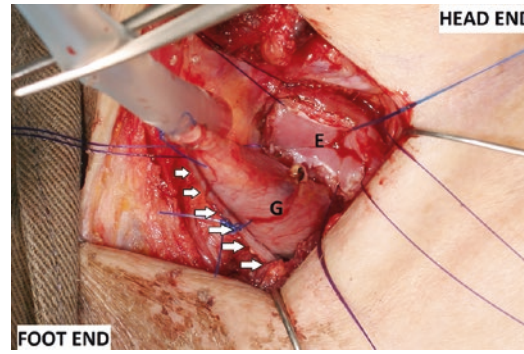

Fig. 11.6 Esophagogastric anastomosis. *E* Proximal esophageal stump opened up with stay sutures, anchoring at 4 corners at 3, 6, 9, 12 o'clock position. Extra suture in blue is the temporary anchoring stitch for the decompression tube. *G* Tip of gastric conduit connected to a chest tube that has been pulled up via the posterior mediastinal route. White arrows: the staple line along the lesser curvature which is now facing anteriorly

Recurrent Laryngeal Nerve Injury

The importance of lymphadenectomy around the recurrent nerves cannot be overstated. On the other hand, the risk of vocal cord paralysis after esophagectomy can be as high as 60–70%. Due to the variability of the anatomy of the recurrent nerves and their high sensitivity to thermal and traction injury, technology has helped us to confidently identify the nerves and potentially prevent the injury. Intermittent recurrent nerve monitoring has been well documented in thyroid surgery. The same can be applied to esophagectomy with a longer probe and a ball tip to accustom to the deep thoracic cavity. The newer continuous nerve monitoring system works through autonomic periodic stimulation of the vagus nerve to ensure the completeness of the circuit. Any drop in the amplitude of the electromyography of the vocalis muscle or the latency of nerve conduction beyond the threshold will trigger an alarm to notify the surgeon of potential nerve injury. The authors believe that nerve monitoring can help the surgeon to improve the quality of lymph node dissection and prevent potential complications (Fig. 11.7).

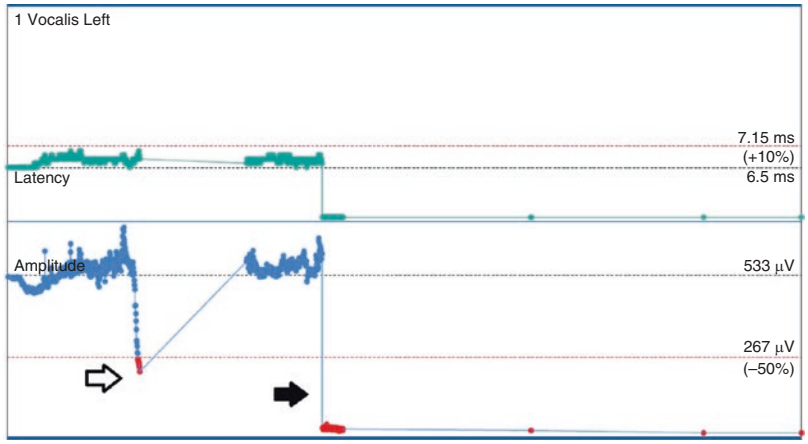

Fig. 11.7 Continuous intraoperative left recurrent laryngeal nerve monitoring—autonomic periodic stimulation reading. White arrow: a transient drop in amplitude for more than 50% of baseline in left vocalis electromyography. It can be due to minor traction. Black arrow: permanent drop in both latency and amplitude to minimal reading. It can be due to transection of the nerve or dislodgement of vagus nerve probe

Gastric Conduit Ischaemia

Conduit ischaemia although rare, is a potentially lethal complication. Patients surviving the initial sepsis would have prolonged hospitalization, repeated operations, delayed adjuvant treatment, and significant residual morbidity. Traditionally, determination of conduit vascularity relies mostly on naked eyes assessment on its colour, turgor and back bleeding at cut edges. Various methods have been utilized to enhance the detection rate (e.g. laser doppler flowmetry, transmural oxygen saturation, spectrophotometry, etc.) but none has shown to be reliable. Indocyanine green angiography has gained its popularity in recent years to provide a real-time quantitative assessment of conduit vascularity. Depending on the different hardware and software available in the market, some may give fluorescence or superimposed coloured images for surgeons to determine the cut-off for satisfactory blood supply. Data analysis can show detailed inflow and outflow velocity of Indocyanine green at a particular site of the conduit. The intraoperative decision can be altered and the site for anastomosis with satisfactory perfusion can be determined with confidence (Fig. 11.8).

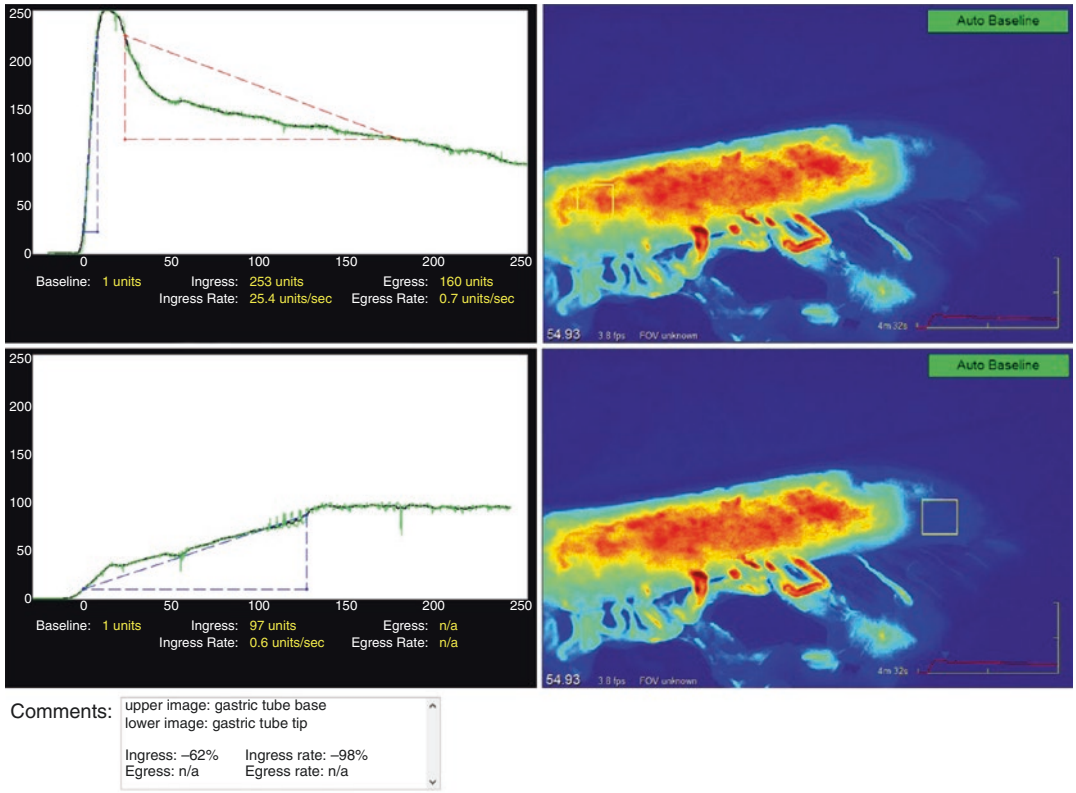

Fig. 11.8 Software for ICG perfusion data analysis. Upper images with "square" placed at distal (antral) end of the gastric conduit, showing good ingress and egress of ICG as demonstrated by the steep slopes in the graphs. Lower images with "square" placed at proximal (fundal) end of the gastric conduit, showing slow ingress and no egress of ICG. The poorly perfused segment is resected and anastomosis should be placed at site balancing the optimal perfusion adequate length of the conduit

Conclusions

The surgical technique on three-phase esophagectomy has evolved throughout the years but the basic concept persisted. A good surgical outcome depends on patient selection, surgical skills, prevention of complication, and vigilance in the management of potential complications. New technology on energy device, stapling device, and other adjuncts has helped the surgeon to perform a safer, if not better, surgery.

En Bloc Esophagectomy

12

Steven R. DeMeester

Vagal-Sparing Esophagectomy

The technique for a vagal-sparing esophagectomy was described in the 1980s by Professor Akiyama from Japan [1]. We have adopted this technique for patients with either high-grade dysplasia or intramucosal cancer who have failed or were not interested in endoscopic therapy for this lesion. In these patients we have confirmed vagal integrity, and found a significant reduction in the prevalence of dumping and diarrhea compared to patients that had a standard esophagectomy with vagotomy [2, 3]. The vagal-sparing procedure is only applicable to patients with high-grade dysplasia or intramucosal (T1a) tumors since no lymphadenectomy is performed. In patients with a visible lesion it is critical to confirm that the tumor is confined to the mucosa since submucosal invasion imparts a significant risk of lymph node metastases and excludes a vagal-sparing approach. Given the inaccuracy of endoscopic ultrasound for determining intramucosal versus submucosal invasion we routinely use endoscopic mucosal resection to definitively stage the depth of tumor invasion of superficial lesions [4]. This allows us to assess the appropriateness of a vagal-sparing esophagectomy for the lesion. The use of a vagal-sparing esophagectomy has markedly diminished with the ability to treat most patients with high-grade dysplasia or intramucosal adenocarcinoma using endoscopic resection and ablation techniques [5].

En Bloc Esophagectomy

The en bloc procedure is typically performed through an initial right thoracotomy followed by a midline laparotomy with a cervical anastomosis via a left neck incision. The thoracic dissection includes removal of the azygos vein with its associated nodes, the thoracic duct, and the low paratracheal, subcarinal, paraesophageal, and parahiatal nodes in continuity with the resected esophagus. The block of tissue removed typically is bounded laterally on each side by the excised mediastinal pleura, anteriorly by the pericardium and membranous trachea, and posteriorly by the aorta and vertebral bodies. The abdominal dissection includes removal of the lymph nodes along the hepatic artery and portal vein from the porta hepatis to the celiac trunk, around the celiac trunk, and along the left gastric artery and lesser curvature of the stomach. In addition, all the retroperitoneal tissue cephalad to the hepatic artery is removed, including the tissue adjacent to the inferior vena cava and the right crus of the diaphragm. On the left side, the tissues and lymph nodes surrounding the splenic artery and the tissue

S. R. DeMeester
The Oregon Clinic, Portland, OR, USA
e-mail: sdemeester@orclinic.com

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overlying the adrenal gland and left crus of the diaphragm are removed. Typically, reconstruction is done with a tubularized stomach graft. However, when a colon interposition is planned for esophageal reconstruction then the abdominal dissection also includes removal of the proximal two thirds of the stomach, the omentum, and the lymph nodes along the proximal two thirds of the greater curvature of the stomach.

The goal of the en bloc resection is to minimize the risk of an incomplete or R1 resection, avoid local-regional recurrence, and maximize the resection of potentially involved lymph nodes. Our initial series of 100 consecutive patients that had primary en bloc esophagectomy was published in 2001 and showed that with surgery alone for esophageal adenocarcinoma overall survival was 52% at 5-years, and was 94%, 80%, 77%, 24% and 29% in patients with AJCC stage I, IIa, IIb, III, and IV tumors respectively [6]. During detailed follow-up (median 40 months) 69% of patients remained free of disease. Systemic disease developed in 31% of patients, but local-regional recurrence occurred in only one patient (1%). Similar excellent local control and survival rates with *en bloc* resection have been reported by Altorki and Skinner [7]. These data serve to refute the nihilistic attitude that esophageal cancer is systemic and incurable at the time of diagnosis, and the low incidence of local recurrence after *en bloc* resection stands in stark contrast to the 20–40% incidence of local recurrence following transhiatal resections [8]. Since local recurrence after esophagectomy typically results in rapid death from cancer, local control remains one of the primary goals of therapy for this disease, and a fundamental goal for surgeons.

The en bloc resection as described above is designed to provide the optimal resection for a distal esophageal adenocarcinoma. Given the rarity of paratracheal and cervical nodal involvement it does not include a three-field dissection. The en bloc dissection is also appropriate for tumors at the gastroesophageal junction since the pattern of lymph node metastases for these tumors is similar to that for a distal esophageal adenocarcinoma [9]. Typically upwards of 25 lymph nodes are removed with the en bloc dissection, often in the range of 40–60 nodes. While this may seem excessive since many esophagectomies remove ten or less nodes, several studies have confirmed the benefit of a more extensive lymphadenectomy on survival. In a multi-center study, we showed that survival was optimized with resection of 23 or more nodes, and that the only operation that reliably achieved that kind of node retrieval was the en bloc resection [10]. These studies have reinforced the value of the en block dissection for curative surgical therapy for esophageal adenocarcinoma.

Currently, most patients with local-regionally advanced tumors undergo neoadjuvant chemo or chemoradiotherapy prior to esophagectomy. The neoadjuvant therapy often shrinks and in some cases completely eradicates the disease. In these patients, some surgeons suggest that the type of resection is not relevant since the neoadjuvant therapy has "cleaned up" the margins and the goal is to just resect the residual primary lesion in the esophagus, if any, and the immediately adjacent lymph nodes. However, in an analysis of survival with transhiatal esophagectomy compared to an en bloc resection in patients that had neoadjuvant therapy we showed that survival was significantly improved with the en bloc approach, particularly for patients with residual disease in their final resection specimen [11]. Interestingly, there was a trend toward improved survival with the en bloc approach even in patients with a pathologic complete response. At first blush, this seems hard to explain since supposedly all the disease was eradicated by the neoadjuvant therapy. Why should the type of resection matter in these patients? There are several studies that shed light on this finding. First, in a study evaluating survival in patients that were node negative after primary resection compared to those that were node negative but had neoadjuvant therapy, there was a marked difference with significantly better survival in the node negative patients after primary resection [12]. This would suggest that there is hidden disease in patients after neoadjuvant therapy, despite a supposed pathologic complete response. Another factor is that pathologists typically evaluate only a small portion of each

resected node using routine H & E staining. In another study we evaluated the frequency of micrometastatic disease in eight patients that were node negative using routine staining [13]. Immunohistochemistry showed micrometastases in three of these eight patients. This indicates that there is often unrecognized nodal disease simply due to the limitations of pathologic assessment of lymph nodes. This study also showed that survival was impacted in patients that had these micrometastatic deposits in lymph nodes, and these nodes were additive to node staging based on routine H & E staining. In light of these studies, the concept that an en bloc resection may improve survival even in patients with pathologic complete response after neoadjuvant therapy makes sense.

Transhiatal Versus En Bloc Resection

Debate continues regarding whether the approach and extent of lymphadenectomy alter the survival for surgically treated esophageal adenocarcinoma. Increasingly there is evidence that it does. We performed a retrospective analysis of a matched series of patients that had either an en bloc or a transhiatal resection for T3N1 esophageal adenocarcinoma and had a minimum of 20 lymph nodes resected and examined [14]. Survival was similar between operations when patients had extensive nodal disease, nine or more involved nodes. This is not surprising since we have previously shown that systemic recurrence is nearly universal in these patients [15]. In contrast, in patients with eight or less involved nodes significantly improved 5-year survival was present in those that had an *en bloc* resection. This is compelling evidence that the type of resection influences survival since all patients were followed a minimum of 5 years, and all deaths were due to cancer. These findings were subsequently confirmed in a randomized control trial comparing en bloc versus transhiatal esophagectomy from the Netherlands [16]. Patients with eight or fewer involved lymph nodes had significantly improved survival with an en bloc compared to a transhiatal esophagectomy. However, with more than eight involved nodes the type of operation did not impact survival. In an analysis of the results for therapy of distal esophageal or GEJ adenocarcinoma in a well-defined and stable Finnish population, Sihvo et al. reported that patients that had an *en bloc* resection with 2-field lymphadenectomy had significantly improved survival compared to patients that had a less extensive resection [17]. Interestingly, their 5-year survival after *en bloc* resection was 50%, which is nearly identical to the 5-year survival reported after *en bloc* resection in other series including ours detailed above. Similarly, the 23% 5-year survival following non *en bloc* resection in their series mirrors what has been reported in numerous other series of transhiatal resections with or without neoadjuvant therapy.

Minimally Invasive Esophagectomy

In the late 1990s surgeons began exploring the potential for a minimally invasive esophagectomy. Techniques have subsequently been developed for a fully laparoscopic as well as a combined thoracoscopic/laparoscopic or Ivor-Lewis type minimally invasive esophagectomy. Disadvantages of the completely laparoscopic approach include the inherent dangers of dissection near the pulmonary vessels and trachea high in the mediastinum, and the inability to accomplish a systematic thoracic lymphadenectomy with this approach. However, the vagal-sparing procedure is ideally suited to a laparoscopic approach since the esophagus is stripped out of the mediastinum without any dissection, and no lymphadenectomy is necessary in these patients with only high-grade dysplasia or intramucosal cancer. For patients with more advanced cancer, the combined thoracoscopic/laparoscopic approach offers the advantage of a thoracic lymphadenectomy. To avoid a neck dissection and the potential for recurrent laryngeal nerve injury many centers favor a minimally invasive Ivor-Lewis approach with intra-thoracic esophago-gastric anastomosis. Importantly, a thoraco-

scopic approach allows a full thoracic systematic en bloc resection to be performed including resection of the thoracic duct and azygous vein, although only a very few highly specialized esophageal centers offer a minimally invasive en bloc resection.

Colonic Interposition

Esophageal reconstruction is often the most challenging component of an esophagectomy, and is certainly the aspect most noted and evaluated by the patient. Unfortunately, there is no replacement organ that is able to mimic the function of a healthy esophagus. Instead, all suffer from a lack of effective peristalsis and the absence of a physiologic barrier to reflux. Despite these shortcomings, available esophageal replacement organs permit most patients to eat very satisfactorily, and in patients who undergo esophagectomy for large tumors or severe strictures swallowing is often significantly improved.

The most common esophageal substitute is the stomach. Advantages of a gastric pull-up include the relative speed and ease with which the stomach can be mobilized, the need for only one anastomosis, and the generally reliable blood supply through the right gastroepiploic arcade along the greater curvature. Disadvantages of a gastric pull-up include the fact that there is often relative ischemia at the tip of the fundus, and the leak and stricture rate of a cervical esophagogasrtic anastomosis can be as high as 30%. In addition, the long-term presence of acid-secreting gastric mucosa juxtaposed to acid-sensitive squamous esophageal mucosa with no intervening barrier can lead to complications of reflux including Barrett's esophagus and adenocarcinoma. Finally, in patients with large tumors near the gastroesophageal junction use of the stomach may compromise the oncologic resection since the gastric staple line along the lesser curve is likely to be within a few centimeters of the neoplasm.

In contrast, use of the colon to replace the esophagus allows an excellent oncologic resection of tumors near the gastroesophageal junction. The colon is acid resistant, and by virtue of its long length it prevents exposure of esophageal mucosa to refluxed gastric juice, thereby decreasing the risk of Barrett's developing in the residual esophagus. Typically, the transverse colon graft has an excellent blood supply via the left colic and marginal artery, and since the tip of the colon graft is well perfused the esophago-colo anastomosis heals reliably in most patients. We have found that compared to an esophago-gastric anastomosis the stricture rate of an esophago-colo anastomosis is significantly decreased [18]. In addition, since the colon is outside the field of radiation for distal esophageal cancers, a colon interposition in patients that have had neoadjuvant chemoradiotherapy allows healthy, non-radiated tissue to be used for the esophageal anastomosis. Another benefit of the colon graft is that length is seldom an issue, even if the reconstruction is at the level of the pharynx. However, compared to a gastric pull-up a colon interposition is more difficult to mobilize, entails three anastomoses rather than one, and takes longer in the operating room. Further, meticulous attention to operative detail is required when using the colon to ensure both short and long-term success with the graft.

Prior to use of the colon for an esophageal substitute a colonoscopy or dual-contrast barium enema should be obtained to assess the graft for polyps or other lesions that should either be addressed prior to the use of the colon for esophageal replacement or that would preclude use of the colon for this purpose. In addition, we often obtain a visceral arteriogram to assess patency of the inferior mesenteric artery, completeness of the marginal artery, and presence of aberrant anatomy including early branching or two middle colic arteries arising from the superior mesenteric artery. A standard colon graft is unlikely to be feasible after repair of an abdominal aortic aneurysm since the inferior mesenteric artery is often ligated during this procedure. Other conditions that discourage use of the colon include ulcerative colitis, extensive diverticulosis, prior diverticulitis, Hirschsprung's disease as an infant, or previous colonic resection.

While important with any esophageal replacement graft, anesthetic management is critical when using a colon interposition. In particular, intravascular volume needs to be adequately maintained, and additional fluids given anticipating the greater third-spacing that accompanies a larger dissection. It is also essential that no pressors or vasoconstrictive agents be given since the small mesenteric vessels of the colon are exquisitely sensitive to these drugs, and spasm or constriction can lead to thrombosis of these small vessels with loss of the graft. Likewise, maintenance of a normal pH and acid-base balance is vital throughout these procedures.

The left, right and transverse colon can be used as interposition grafts. Regardless of the planned graft, the ascending and descending portions of the colon as well as the hepatic and splenic flexures are mobilized. It is helpful to pack the small bowel into a bag to keep it out of the way during mobilization of the colon and dissection of the mesentery. Most commonly, the transverse colon is used in an isoperistaltic fashion and the graft is based on the inferior mesenteric artery, the ascending branch of the left colic artery, the marginal artery of Drummond, and communication between the left and right branches of the middle colic artery. It is critical to maintain communication between branches of the middle colic artery since almost always the proximal extent of the graft is to the right of the middle colic trunk.

When using a colon graft we typically place the anastomosis in the neck. The necessary length of colon is determined by measuring from the left ear to the xiphoid with an umbilical tape. The tape is cut to this distance. Next, the splenic flexure/descending colon is brought up to the hiatus being careful to minimize tension on the left colic vessels, and a 3-0 silk stitch is placed in a tinea as a mark. The umbilical tape is then laid out on the colon starting from the marking stitch and going proximally. Typically, the umbilical tape ends near the hepatic flexure or in the distal ascending colon. A second 3-0 silk marking stitch is placed here, and the colon re-measured to be certain of the stitch placement sites.

The mesenteric dissection commences along the inferior edge of the pancreas at the root of the transverse mesocolon in the lesser sac. Often the middle colic vein can be visibly traced downward into this vicinity, and with careful dissection the superior mesenteric vein (SMV) and the junction with the middle colic vein are identified. In some cases, an accessory middle colic vein is present with a separate entrance into the SMV. An important variant to recognize is one where the gastroepiploic vein joins either the middle colic vein or more commonly the accessory middle colic vein prior to joining the SMV. It is critical to preserve the gastroepiploic vein since this will be the primary drainage of the residual antrum if the colon is used, and is essential if a gastric pull-up is necessary. Next, the middle colic artery is identified and dissected to its origin from the superior mesenteric artery (SMA). It is often easiest to do this dissection by holding the transverse colon up in a cephalad direction while working at the root of the mesentery medial to the ligament of Treitz. The SMA is identified just lateral to the SMV. It is important to identify the middle colic artery at its origin from the SMA to be certain there is not an early bifurcation that would be compromised by dividing the vessel distally. At this point the anatomy is identified, but no vessels are ligated or divided.

Next, the mesentery at the site of the proximal stitch in the colon is dissected, and the colon wall cleaned in preparation for division. Deeper in the mesentery the arcade vessels joining the middle colic circulation with the right colic vessels are encountered. A bulldog clamp is placed on this arcade and the mesentery divided centrally below these vessels and carried toward the middle colic vessels. Generally, this portion of the mesentery is avascular, but occasionally a small arterial or venous branch is encountered. Arterial branches are clamped with fine bulldog or microvascular clamps. The dissection is continued beyond the middle colic vessels toward the ligament of Treitz, and here again the mesentery should be largely avascular. Any small arteries identified should be clamped with a microvascular or bulldog clamp. Care is taken to prevent injury to the inferior mesenteric vein as the splenic flexure region is approached.

Once the distal colon stitch is reached the mesenteric dissection is finished. Now the portion of transverse colon between the stitches is receiving arterial supply only from the ascending branch of the left colic and the middle colic arteries. The pulse in the middle colic artery should be palpated and then a bulldog clamp placed proximally on the middle colic artery at its origin and the pulse rechecked. At this point the graft is perfused only by the ascending branch of the left colic artery. Doppler signals should be ascertained, and the colon inspected for evidence of ischemia. Commonly the distal portion of the graft (the area near the proximal stitch) will spasm initially, but over time it should dilate, and in a good colon the small mesenteric vessels adjacent to the bowel wall will be visibly pulsatile after several minutes with the clamps in place. Recently we use indocyanine green injection to assess perfusion intraoperatively with the SPY device (Novadaq, Toronto CA). Once satisfied with the vascularity of the graft the clamped arteries are ligated and divided as are the corresponding veins. Ideally only a single middle colic artery and vein are ligated, but often an accessory small vein or artery is present and needs to be divided.

The colon itself is then divided at the site of the proximal stitch with a GIA stapler, and the graft held straight up in the air. If the mesentery restricts straightening the graft then it is incised, often tangentially, using transillumination to avoid any vessels. This will usually allow the graft to be nearly straight. The graft can then be tucked into the pelvis while the esophageal resection is performed.

The colon graft can be placed in either the posterior mediastinal or a substernal position. The graft is pulled through the designated space carefully wrapped in a camera bag to minimize trauma and maintain anatomic alignment. Once the graft is passed up to the neck an end-to-end esophago-colo anastomosis is performed with a single layer of full-thickness 4-0 monofilament absorbable sutures. Size discrepancy must be taken into account, although with dilatation of the esophagus secondary to distal obstruction the size match is often close. After completing the proximal anastomosis the graft is pulled firmly down into the abdomen. This is facilitated by removal of the camera bag used to pull the graft up to the neck. An important next step it to suture the colon graft to the left crus of the diaphragm at the hiatus with several permanent sutures. This will help prevent intrathoracic redundancy of the graft and also prevents herniation of other abdominal organs into the posterior mediastinum. Failure to secure the colon graft to the left crus of the diaphragm likely contributed to the relatively high reoperation rates for redundancy reported by some centers.

When the graft is placed substernally it is recommended that the thoracic inlet be opened by removing the left half of the manubrium, clavicular head, and the medial portion of the left 1st rib in order to accommodate the graft and prevent compression as it transitions from the posterior neck to a substernal location. Similarly, the exit from the substernal tunnel should be inspected. It is advisable to separate the diaphragm from the undersurface of the sternum and medial portions of the thorax anteriorly to create space for the graft. If the left lateral segment of the liver is large it may be necessary to excise it to prevent interference with the course of the graft as it descends to join the gastric remnant. Further, in some patients the pericardium acts as a shelf and leads to acute angulation of the graft as it descends to join the gastric remnant. This angle can be softened if necessary by opening the pericardium in an anterior-posterior direction and then closing it transversely. The colon should be sutured to the left portion of the diaphragm to again prevent redundancy and herniation of abdominal viscera into the substernal space.

The distal colon graft is then divided with a GIA stapler preserving about 10 cm of intra-abdominal colon below the hiatus. Excess intra-abdominal colon can lead to stasis and regurgitation and must be avoided. Great caution is used when dividing the colon to prevent injury to the underlying mesenteric vessels supplying the graft. Unless the vagus nerves are spared the stomach is divided leaving only the antrum, and a pyloroplasty is performed. The colo-gastric anastomosis is completed using two layers of 3-0 silk sutures. When the vagus nerves are preserved

only the gastroesophageal junction is excised, and no pyloroplasty is necessary. In this circumstance, the proximal short gastric vessels are divided to allow passage of the colon graft from the hiatus to the posterior aspect of the stomach, and a stapled colo-gastric anastomosis is performed to the posterior gastric body.

The final step is the colo-colostomy. When using the transverse colon this anastomosis ends up in the left upper quadrant near the colo-gastric anastomosis. Sometimes is necessary to mobilize the distal colon a few centimeters to facilitate performance of this anastomosis, but again caution is necessary to avoid injury to the mesenteric vessels supplying the graft and to prevent ischemia of the mobilized end of the colon. A nasogastric tube is carefully passed into the stomach, the mesenteric defect is closed, and a feeding jejunostomy is placed.

Trouble Shooting During Colonic Interposition

Numerous aberrances are possible in the circulation to the transverse colon, and some are commonly encountered. One is the joining of the right gastroepiploic vein to either the middle colic vein or an accessory vein prior to joining the SMV. This vein must be preserved. Another common problem is proximal bifurcation of the middle colic artery into left and right branches. The communication between these vessels must be maintained, so ligation of the middle colic artery needs to be proximal to the bifurcation. In some cases a side-biting clamp must be applied to the SMA in order to divide the middle colic vessel and preserve the communication between left and right branches. However, in some patients there are two completely separate origins of the middle colic artery from the SMA. In these patients either a different portion of colon is used and the graft is based on the middle colic vessels, or one of the divided middle colic arteries is anastomosed to the internal mammary artery or a neck vessel to supercharge the graft. Our experience has been that when two separate middle colic arteries are present the graft is at high risk for ischemia and it would be unwise to use it without supercharging. Two veins are relatively common, and provided one is small and there is visible collateral communication between the veins it seldom poses a problem for the graft. However, three veins or no clear communication between two major vein branches should be cause for significant concern. In this circumstance, consideration should be given to either abandoning the colon graft or performing a microvascular anastomosis between one of the middle colic veins and the innominate vein with the colon in a substernal location. Regardless of the arterial and venous anatomy, the absence of a Doppler signal at the proximal end of the graft is also an indication to supercharge the graft, perform an esophagostomy and reinspect the colon at about 48 h, or abandon the transverse colon and use an alternate conduit.

If the transverse colon is not available or suitable for use, the right or left colon can be used as an interposition graft. Compared to the left colon the right colon is thin walled and bulky. It can be used in an isoperistaltic fashion based on the middle colic vessels, and is a reasonable choice if colon is required and there are two independent middle colic arteries arising from the SMA. The right colon including the cecum will usually reach to the neck, but if not a portion of terminal ileum can be left attached to the cecum. The ascending colon graft relies on an intact arcade between the right branch of the middle colic and the right colic artery.

The left colon is also a suitable conduit, and the wall thickness and caliber of the lumen of the left colon make it more suitable for esophageal replacement than the right colon. The drawback to use of the left colon is the requirement that it be used in a retroperistaltic fashion based on the middle colic vessels, and the greater propensity for the descending colon to be involved with diverticulosis.

Conclusions

The en bloc resection, done either as an open or minimally invasive procedure, provides optimal local control and superior nodal resection compared to alternative types of esophagectomy. These factors translate into improved

survival in patients with limited N1-2 nodal disease. However, the high risk for systemic disease precludes a benefit for the en bloc resection in patients with extensive N3 nodal disease. Reconstruction is typically with a gastric pull-up, but the colon is an excellent alternative graft.

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13 Fundamentals of Minimally Invasive Esophagectomy

Kirsten Newhams and Blair A. Jobe

Selecting an Operative Approach: Open Versus Minimally Invasive Esophagectomy

As more surgeons pursue minimally invasive approaches to esophagectomy, the volume of data regarding outcomes has increased. Meta-analysis studies have shown reduced blood loss, fewer respiratory complications and improved overall survival associated with MIE. Operative times, however, can be longer than an open approach. From an oncologic standpoint, there was no significant difference between lymph node harvest or R0 resection. Recent updates on earlier randomized controlled studies comparing MIE and open esophagectomy have shown no difference in disease-free and overall survival [1–7]. Ultimately, the decision on approach is based upon the surgeon's experience and preference.

Minimally Invasive Esophagectomy

There are no formal contraindications to a minimally invasive approach beyond a patient's ability to withstand pneumoperitoneum, and certain considerations such as prior abdominal or thoracic surgery or bulky disease. Despite a growing embracement of minimally invasive techniques, esophagectomy remains a physiologically taxing operation with high morbidity rates. Preoperative optimization is key to improve perioperative outcomes. In particular, the use of dedicated preoperative dietary counseling paired with supplementation through either protein drinks or additional enteral nutrition with a feeding tube jejunostomy for malnourished patients, serve to bolster the nutritional status of the patient. Additionally, immunonutrition started 5 days prior to esophagectomy has become a mainstay in our practice. For patients who present in a deconditioned state, consideration should be made for preoperative physical therapy and pulmonary rehabilitation, when indicated. After preoperative staging is completed, a decision can be made regarding a particular minimally invasive approach. The selection of the approach is based on patent disease as well as surgeon preference, training, and experience.

Intraoperative Considerations

To further optimize patient outcomes, intraoperative considerations are critical and require dedicated communication with the anesthesia team. In particular, judicious fluid and vasopressor management are required to limit volume

K. Newhams · B. A. Jobe (✉)
Esophageal and Lung Institute, Allegheny Health Network, Pittsburgh, PA, USA
e-mail: Kirsten.Newhams@ahn.org; blair.jobe@ahn.org

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overload and deleterious vasoconstriction. Invasive hemodynamic monitoring generally can be done through an arterial line. Double lumen endotracheal intubation is necessary to provide single lung isolation for the thoracic component of the operation. Lastly, adequate pain control should begin intraoperatively to further manage the patient's physiologic response to surgery.

Stage I: Abdomen

The operation typically should begin with endoscopic and possibly bronchoscopic re-evaluation. This initial step serves to re-establish the patient's anatomy and assure resectability. Following this, the patient can be positioned for the abdominal component of the operation.

The patient is placed in a supine position with arms out and a padded foot board in place. Insufflation is achieved with a Veress needle placed along the left subcostal margin. A total of five ports are placed in the upper left and right quadrants, including a 5 mm port placed to the left of the xiphosternum and a 10 mm port in the upper right quadrant. The remaining ports are 5 mm (Fig. 13.1).

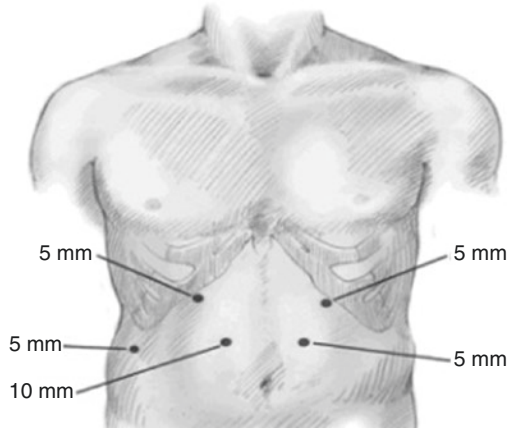

Fig. 13.1 Port placement for abdominal stage of MIE. Standard port placement includes a total of five ports across the upper left and right quadrants. A 10 mm port is placed in the upper right quadrant just off midline with remaining 5 mm ports placed along the right and left subcostal margins

A Nathanson liver retractor is introduced through the xiphoid port and secured to a post affixed to the bed at the patient's right axilla.

The gastric mobilization is begun with division of the gastrohepatic ligament. The division of the ligament is carried cephalad to the right crus. This dissection is carried anteriorly and along the left crus, dividing the phrenoesophageal ligament in the process. If the operation is being performed for malignant disease, it is important to include a cuff of the peritoneum from the diaphragm with the dissection. A retroesophageal window is created and a Penrose drain is inserted through it to elevate the esophagus and thereby divide the remaining posterior-lateral attachments. The anterior and posterior vagus nerves are identified at this point and divided, providing additional intra-abdominal esophageal length and allowing for further mobilization. It is important to limit mediastinal dissection at this time so as to prevent entry into the pleura and a subsequent prolonged pneumothorax with hemodynamic instability.

The stomach is elevated anteriorly and the left gastric pedicle is identified. The associated fibrofatty lymphatic tissue is bluntly swept towards the stomach. Using the vascular load of a stapler, the pedicle is divided.

Following this, attention is turned to the greater curvature. The watershed area of the left and right gastroepiploic vascular arcade is identified and the omentum is opened lateral to this location, thus preserving perfusion of the future gastric conduit. The division of the gastrosplenic ligament is carried cephalad beyond the spleen to the level of the left crus. The posterior stomach is grasped and elevated laterally and folded back medially, revealing the remaining posterior gastric arcade and attachments, which are divided, achieving complete proximal gastric mobility.

The gastrocolic division is completed next. It is critical to identify and avoid the gastroepiploic vessels, as they will maintain perfusion to the future conduit. The dissection is carried from the patient's left in the direction of the gallbladder, just beyond the pylorus (Fig. 13.2).

If a gastric emptying procedure is to be performed, two stay sutures are placed at the 12

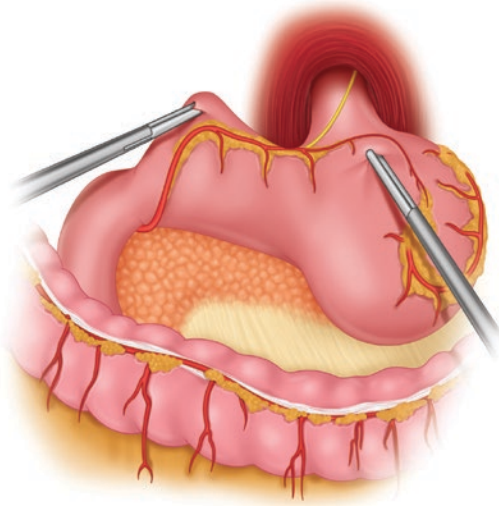

Fig. 13.2 Division of the gastrocolic ligament. The gastrocolic ligament is divided along the greater curvature, starting at the watershed area of gastroepiploic vessels and carried beyond the pylorus. It is imperative to avoid injury to the gastroepiploic vessels that will serve as perfusion to the gastric conduit

o'clock and 6 o'clock positions flanking the pylorus. The pylorus is then divided longitudinally with an ultrasonic scalpel to the duodenal bulb. The closure is then completed in a transverse fashion (i.e. Heineke-Mikulicz pyloroplasty) (Fig. 13.3).

Now that the stomach is mobilized, the conduit can be fashioned. A location on the lesser curvature 6 cm proximal to the pylorus muscle is selected for the initial site of conduit creation; however, this location can be adjusted based on the tumor location and the need to achieve a negative distal margin. A GIA stapler is used to make the initial division, extending only partially onto the stomach for approximately 1 cm. The stomach is positioned with the fundus gently pulled towards the spleen. Proper retraction is critical in order to maintain a consistent shape to the conduit and prevent a "spiraled staple line" with resultant ischemia. Sequential staple loads are taken cephalad, maintaining an approximately 4–5 cm diameter conduit (Fig. 13.4).

The stomach is completely divided at this point. Indocyanine green can be used with fluorescence imaging to assess conduit perfusion. The two separated aspects of the divided stomach are secured together, maintaining anatomic configuration of the conduit so that it is oriented properly when delivered into the thoracic chest cavity (Fig. 13.5).

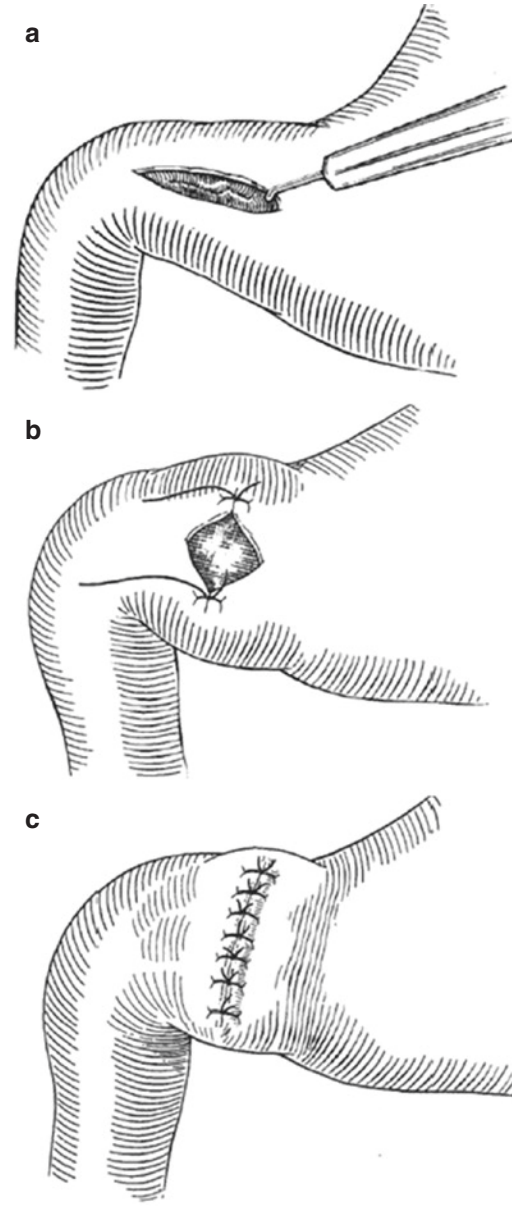

Fig. 13.3 (**a**) Longitudinal opening of the pylorus, (**b**) Stay sutures at 12 and 6 o'clock, (**c**) Transversal closure. Reproduced with permission from Atlas of Esophageal Surgery, P. Marco Fisichella, Marco G. Patti editors, Springer

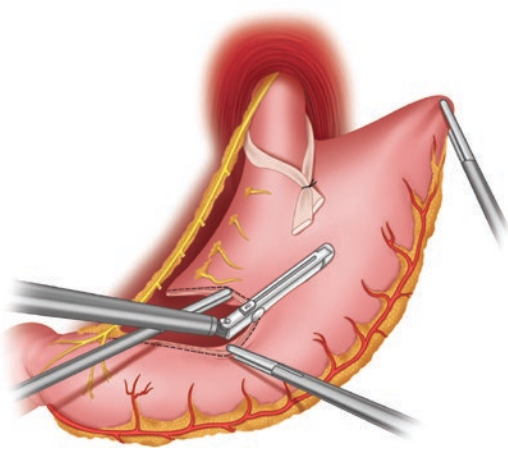

Fig. 13.4 Construction of gastric conduit. The creation of the gastric conduit requires careful attention to positioning of the stomach as it is sequentially divided

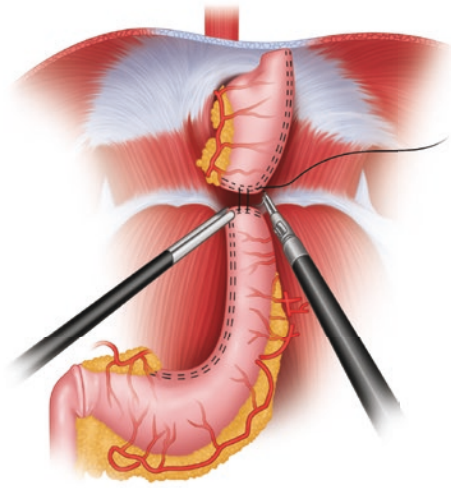

Fig. 13.5 Attachment of gastric conduit to the specimen. After creation of the gastric conduit, it is secured with a U-stitch to the proximally-divided stomach to allow for delivery into the thorax

If the patient did not have a feeding jejunostomy placed preoperatively, it can be placed at this point. Two additional ports are placed in the lower right quadrant. The jejunum is measured 30–40 cm distally from the Ligament of Treitz. Using an interrupted suture placed on the anti-mesenteric border, the jejunum is secured to the anterior abdominal wall at a point that does not create tension. A finder needle is placed through the anterior abdominal wall, into the anti-mesenteric border of the jejunum. Air can be insufflated through the needle to confirm an intra-luminal position. A wire is then advanced through the needle and into the jejunum. A dilator and sheath are placed over the wire and into the jejunum. The wire and dilator are removed and the feeding jejunostomy catheter is introduced through the sheath. Small amounts of insufflated air through the catheter can be used to facilitate advancement of the tube. The sheath is removed and visual confirmation is completed to assure proper positioning. A circumferential purse-string suture is placed along the abdominal wall and anti-mesenteric border of the jejunum, thus securing the jejunostomy tube in place. A second suture is placed just distal to this to secure the jejunum to the anterior abdominal wall, preventing torsion of the bowel.

Attention is then turned to the hiatus, where mediastinal dissection can now be completed. The esophagus is circumferentially dissected free of its distal mediastinal attachments to at least 5 cm proximally, allowing ease of delivery into the thorax. Hemostasis is assured and all ports are removed and trocar sites closed according to surgeon preference.

The patient is now prepared for transition to the thoracic component of the operation.

Stage II: Thorax

Positioning of the patient for the thoracic portion should be completed efficiently in the setting of an established pneumothorax created during the mediastinal dissection. The patient is placed in a left lateral decubitus position on an inflatable bean bag. Care should be taken to properly pad the patient's bony prominences and susceptible nerves. The right arm should be gently elevated across the body in a neutral position and supported appropriately. Bronchoscopy can be completed to confirm appropriate position of the double lumen endotracheal tube. The right lung is isolated.

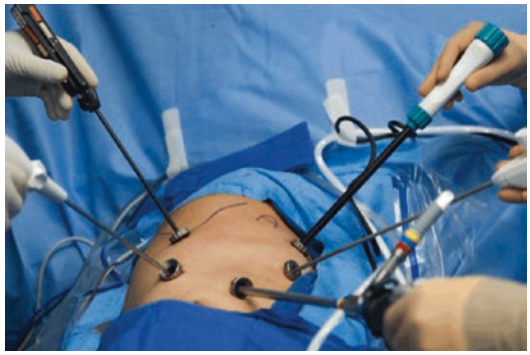

Fig. 13.6 Trocar placement for thoracic stage of MIE. Three 10 mm trocars are placed along the anterior axillary line at the eighth intercostal space, at the tenth intercostal space posterior to the posterior axillary line, and along the anterior axillary line in the fourth intercostal space. A 5 mm port is placed just beyond the tip of the scapula with a final 5 mm port placed along the anterior axillary line between the two 10 mm ports

A 10 mm trocar is placed along the anterior axillary line at the eight intercostal space. Single lung isolation is completed, the thoracoscope is introduced, and the thorax is explored for metastatic disease. Insufflation may be used if desired. A second 10 mm trocar is placed in the tenth intercostal space posterior to the posterior axillary line. A 5 mm port is placed just beyond the tip of the scapula. An additional 10 mm port is placed along the anterior axillary line in the fourth intercostal space with a final 5 mm port placed along the anterior axillary line between the two 10 mm ports (Fig. 13.6).

Next, a suture is placed through the central tendon of the diaphragm, brought out through an incision in the right anterior axillary line in the lower chest and secured with a clamp. This maneuver provides retraction and improved visibility of the hiatus. An adjustable fan retractor is used to bring the lung anteriorly. The inferior pulmonary ligament is divided. Following this, the posterior mediastinal pleura is opened alongside the esophagus and carried cephalad to the azygos vein. Through the course of this dissection, it is important to avoid injury to the thoracic duct. Once the azygos vein is reached, it is divided with a vascular stapler. Dissection then is carried

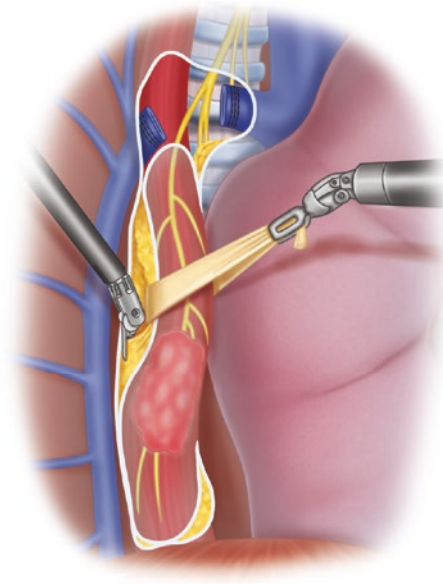

Fig. 13.7 A Penrose drain can be used to encircle the esophagus, which facilitates the dissection during the thoracoscopic phase of the operation

to the level of the thoracic inlet, avoiding injury to the recurrent laryngeal nerve.

Attention then is directed back to the hiatus. A plane is created between the pleura and pericardium. This dissection is carried along the right membranous bronchus, capturing associated lymph nodes with the esophagus within level 7. A circumferential dissection is completed and a Penrose drain can be used to encircle the esophagus (Fig. 13.7). With this move, the remaining esophageal attachments can be divided. As they are encountered, perforating vessels from the aorta and lymphatics can be clipped or divided with an energy device. After the esophagus is circumferentially freed of its attachments, the abdominal esophagus and stomach, attached to the conduit can be delivered into the thorax. If a cervical anastomosis is planned, then the surgeon proceeds with the third stage of the operation.

When an intrathoracic anastomosis is planned, the healthy proximal esophagus is divided with a stapler at the level of the azygous vein.

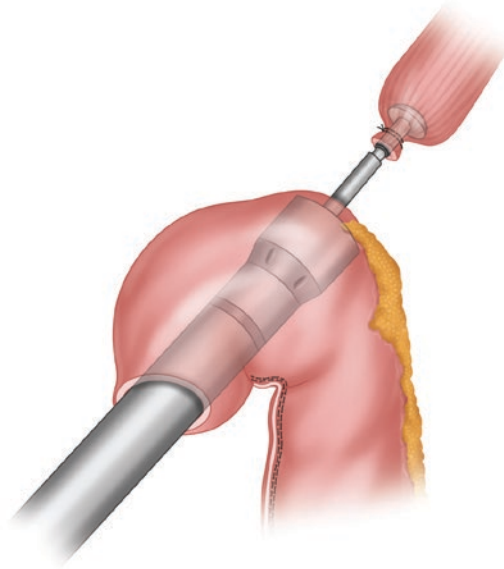

Fig. 13.8 Thoracic end-to-side stapled anastomosis. A "foot-into-sock" approach is undertaken. Confirm proper positioning of the conduit prior to deploying the pin at the greater curvature so as to prevention torsion

The surgeon right hand port is extended to 5 cm and a wound protector is placed. The conduit is then detached from the specimen and delivered through this port. Proximal and distal margins are sent for frozen section pathology evaluation.

The 25 mm anvil attached to a delivery tube is introduced trans-orally and advanced into the proximal healthy esophagus until the anvil is brought to the esophageal staple line. Next, using the ultrasonic scalpel, a gastrotomy is made in parallel with the staple line at the most proximal aspect of the conduit. A 25 mm circular end-to-end anastomosis stapler is introduced into the chest through the surgeon right hand port and into the gastrotomy. The stapler is then advanced distally into the lumen of the conduit, and the proper length and tension are gauged for anastomosis. The stapler pin is then deployed through the greater curvature side of the conduit and engaged into the anvil, and an end-to-side anastomosis is created (Fig. 13.8).

The remaining gastrotomy and redundant gastric conduit are divided with a stapler. An endoscopy can be performed at this point to check for a leak and placement of a nasogastric tube.

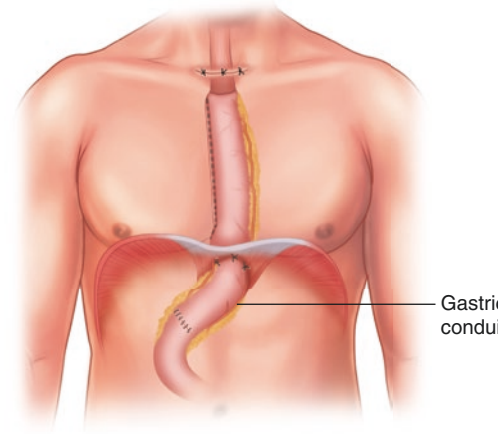

Fig. 13.9 Gastric conduit with a thoracic esophagogastric anastomosis

A 10 mm flat closed suction drain is placed at the level of the anastomosis and exited in the right lower chest in the anterior axillary line. A multilevel intercostal nerve block is performed under thoracoscopic guidance. A 28 French chest tube is placed apically and its position is monitored as the right lung is inflated.

Figure 13.9 illustrates the gastric conduit with a thoracic esophagogastric anastomosis.

Stage III: Cervical

When a cervical anastomosis is pursued, the patient again is placed in a supine position with the head turned to the right and stabilized. The anterior border of the sternocleidomastoid is identified and a 5 cm incision is performed along this point. The sternocleidomastoid is retracted posteriorly, revealing the omohyoid muscle, which is divided. At this point, it will be possible to establish a plane between the carotid sheath and trachea. If the middle thyroid vein is encountered, it can be divided. The plane is further developed until the anterior body of the vertebral body and posterior wall of the esophagus are revealed. The dissection plane should be carried inferiorly until it meets the thoracic dissection plane. The specimen is then delivered in its

entirety through the cervical incision bringing with it the conduit. The proximal esophagus is divided, thus freeing the specimen.

The cervical anastomosis is now performed. A 1.5 cm gastrotomy is made anteriorly along the gastric wall. The divided esophagus is brought inferiorly to meet the stomach. The posterior aspect of the esophagus is aligned with the anterior gastric wall. Two stay sutures are placed to facilitate this alignment. The GIA staple load and anvil are each introduced into either the gastric conduit and divided esophagus. The gastrotomy and esophagotmy are closed with a 2 layer hand-sewn technique. A 10 French closed suction drain is placed within the incision. The wound is closed in layers over the drain.

Completion endoscopy is undertaken for final evaluation of the anastomosis and placement of a nasogastric tube. Lastly, a bronchoscopy is completed to clear the airway of pooled secretions.

Postoperative Care

The nasogastric tube is left in place until output clears and declines or until an esophagram is completed, typically between postoperative days 4–6. A closed suction drain placed at the time of surgery is pulled out 1–2 cm and re-secured on postoperative day 5 or once the esophagram has been completed. Tube feeds through the jejunostomy typically are begun between postoperative days 1–3. They are started at a low rate and slowly advanced based on patient tolerance.

The postoperative care of esophagectomy patients requires a dedicated, coordinated multi-disciplinary approach that leads to an evidence-based patient care pathway. Key components of postoperative care include: early mobilization, limiting volume overload, cautious vasopressor use, pulmonary hygiene, multi-modal pain control that limits opioids, early enteral nutrition and venous thromboembolism prevention. Establishing institutional patient care pathways facilitates communication with the care team that includes dieticians, physical and occupational therapists, respiratory therapists, and intensivists.

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Minimally Invasive Ivor Lewis Esophagectomy

14

Simon R. Turner and Daniela Molena

Introduction

Minimally invasive Ivor Lewis esophagectomy (MIE) is a technically challenging procedure, requiring advanced skills in both thoracoscopy and laparoscopy. With experience, the procedure can be performed with excellent patient outcomes, both in terms of perioperative morbidity and oncologic efficacy, with only a modest increase in operative time compared to open approaches [1–6]. By avoiding open incisions, especially with the thoracotomy, the minimally invasive approach results in less pain and blood loss and fewer pulmonary complications [4, 5, 7–9]. Accordingly, length of stay is also reduced [5, 7, 9]. There is no difference in anastomotic leak rate [5–9], though some studies have demonstrated a small but significant increased need for reoperation compared to open esophagectomy [4, 6]. Importantly, oncologic outcomes, including completeness of resection, number of nodes removed, recurrence, and 3- and 5-year survival appear equivalent, if not improved with minimally invasive esophagectomy [7–9]. Potential oncologic benefits of the minimally invasive approach include improved visualization for more complete lymphadenectomy, especially in obese patients, and less immune dysfunction related to surgical stress and blood transfusion. Quality of life at 1 year is also improved compared to open esophagectomy [10].

Operative Technique

The patient is intubated with a left-sided double lumen endotracheal tube, and two large bore IVs, a radial arterial line and urinary catheter are inserted. If the patient has not had a recent upper endoscopy prior to surgery, this is performed prior to making incisions to determine the extent of the tumor and any associated Barrett's esophagus, to confirm the suitability of the stomach as a conduit and assess the patency of the pylorus. Minimize the amount of air insufflated into the stomach, which will hinder laparoscopy. The stomach is suctioned out with the scope and an orogastric tube is placed to completely decompress the stomach.

The patient is positioned supine on a bean bag. The feet are secured to a padded footboard with tape. The arms are comfortably abducted to allow access to the abdomen. The abdomen is widely prepped and draped. Reverse Trendelenburg position, used during laparoscopy to aid in

S. R. Turner
University of Alberta, Edmonton, AB, Canada

D. Molena (✉)
Thoracic Surgery Service, Department of Surgery,
Memorial Sloan Kettering Cancer Center,
New York, NY, USA
e-mail: molenad@mskcc.org

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visualization of the upper abdomen, is introduced gradually to avoid sudden hypotension.

Abdominal Port Placement

A 10 mm port is placed under direct visualization just under the left costal margin in the mid-clavicular line; after abdominal insufflation with CO_2 at 15 mmHg the other ports are placed as followed: a 10 mm port in the midline just below the falciform ligament, a third 10 mm port in the right flank and a 5 mm port in the right upper quadrant such that instruments will have an easy trajectory under the liver and falciform ligament and towards the hiatus. An optional additional 5 mm port may be placed in the left upper quadrant for the assistant. A Nathanson liver retractor is placed just below the xiphoid to elevate the left lobe of the liver and expose the hiatus (Fig. 14.1). Most of the work is done by the primary surgeon standing on the patient's right, with an atraumatic grasper in the left hand and Harmonic scalpel (Ethicon, Somerville, NJ) in the right. The first assistant stands at the patient's left and uses a grasper in each hand to assist with retraction. The camera operator stands to the patient's right below the primary surgeon. Mobilization of the greater curvature of the stomach, especially the division of the gastrocolic ligament, is done by the surgeon standing on the patient's left.

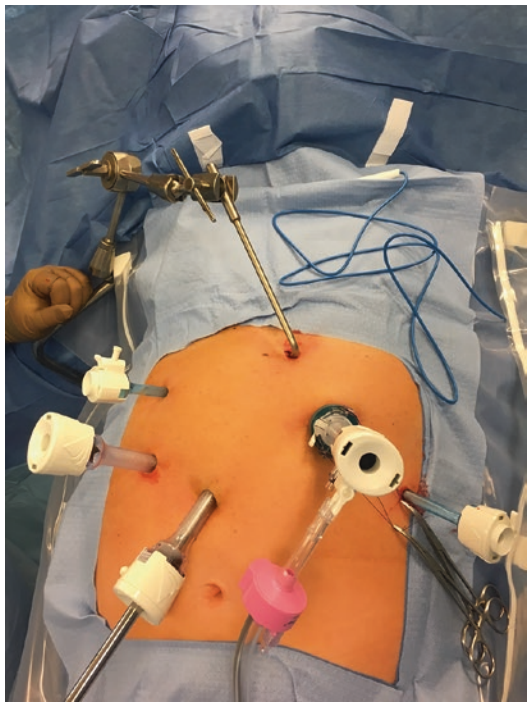


Fig. 14.1 Abdominal port placement

Abdominal Lymphadenectomy and Gastric Mobilization

The dissection begins with division of the gastrohepatic ligament, proceeding superiorly until reaching the right crus. The left gastric, splenic and common hepatic arteries are identified in order to perform a complete dissection of their associated nodes. Dissection is started at the superior aspect of the pancreas and the hepatic artery is identified. This artery is skeletonized superiorly to the takeoff of the left gastric and splenic arteries. Once the left gastric artery is identified, the lymph nodes are swept upwards into the specimen so that the artery and vein can be divided at their origin using a vascular stapler (Fig. 14.2). By retracting the stomach anteriorly, access is gained to the celiac artery nodes found between the left gastric artery stump and the base of the diaphragmatic crus.

Attention then returns to the hiatus. The dissection is carried to the base of the hiatus and into the posterior mediastinum. The left crus is dissected from phrenoesophageal attachments toward the angle of His. Fibers of the crura should be preserved if possible while staying wide enough to ensure an adequate radial margin from the tumor. Muscle of the crura may be resected en bloc if there is concern for invasion by bulky disease at the gastroesophageal junction. The hiatus should be repaired in case of partial resection or when a large paraesophageal hernia is encountered. Leaving a large diaphragmatic crural opening will likely lead to paraconduit herniation of abdominal content into the mediastinum, a complication more commonly seen with minimally invasive esophagectomy, possibly due to lack of intraabdominal adhesions. The esophagus should

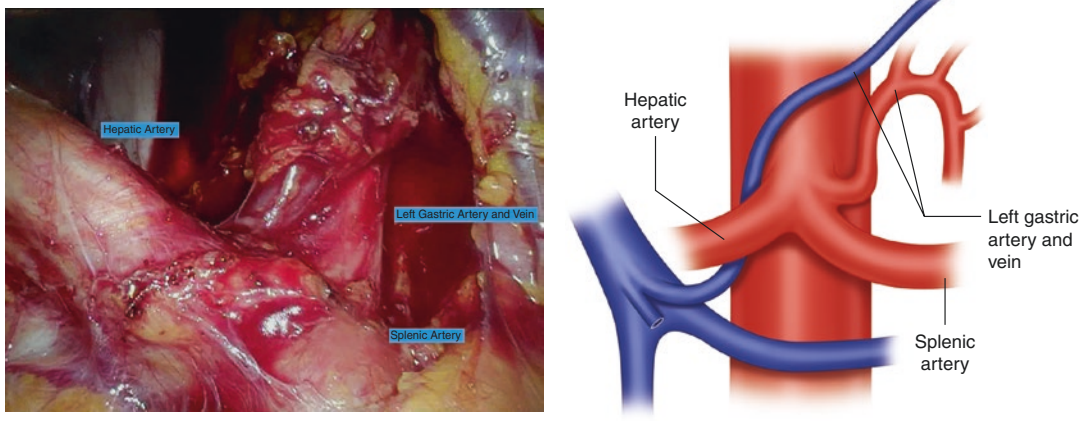


Fig. 14.2 The hepatic and splenic arteries are skeletonized superiorly and the left gastric vessels are completely dissected at their base before division with vascular stapler

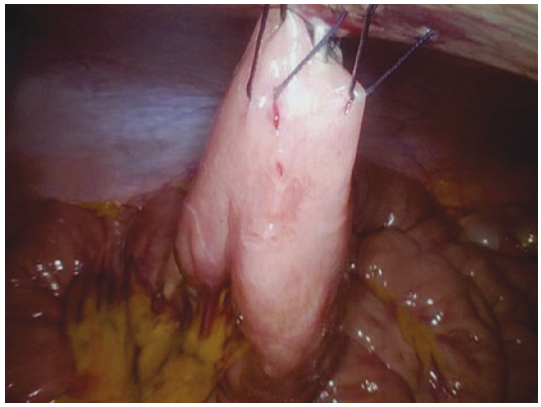
not be completely encircled at this time, nor should extensive transhiatal dissection yet be performed, to avoid pneumothorax and hemodynamic instability early in the procedure.

Careful handling of the stomach throughout the procedure will help preserve the submucosal collateral vessels that are the only vascular supply of the conduit in the area of the anastomosis. Attention is turned to dissecting the greater curvature of the stomach. The stomach is gently retracted anteriorly and to the right, exposing the gastrocolic ligament. The right gastroepiploic artery is visualized and must be preserved to perfuse the gastric conduit. Staying well away from this artery, the gastrocolic ligament is divided along the greater curve toward the fundus. Eventually the artery terminates, though there are sometimes horizontal collaterals with one or two short gastric arteries which should be preserved. Above this level, it is safe to stay closer to the stomach. Doing so allows the short gastric arteries to be divided with a long stump on the splenic side. Care is taken not to injure the spleen as mobilization continues towards the previous dissection along the left crus. It is generally easier to divide the last attachments holding the fundus while standing at the patient's left. If posterior attachments of the stomach to the retroperitoneum are encountered these can now be divided. Posterior gastric arterial branches may also be identified and divided.

Once the fundus is completely mobilized, division of the gastrocolic ligament is continued caudally towards the pylorus. Fully dividing these attachments between the distal stomach and the colon reduces tension on the anastomosis and helps decrease the risk of colonic herniation via the hiatus. The pylorus should be freely mobile and the colon completely separated from the stomach and proximal duodenum. The pylorus will nearly reach the hiatus and a Kocher maneuver is neither required nor encouraged, as excessive duodenal mobility may result in herniation of the duodenum into the chest with kinking of the gastric conduit.

Pyloric Drainage and Feeding Jejunostomy

A pyloric drainage procedure is not necessary in every patient. The decision should be individualized based on the endoscopic appearance of the pylorus during preoperative gastroscopy. If the pylorus is widely patent at baseline no drainage procedure is necessary. If not, 100 units of Botox in 5cc of sterile saline are injected into the muscle of the pylorus using a transabdominal needle. Botox temporarily allows free drainage of the conduit while function is at its worst immediately postoperatively. Eventually, as patients learn to accommodate their new anatomy the effect of



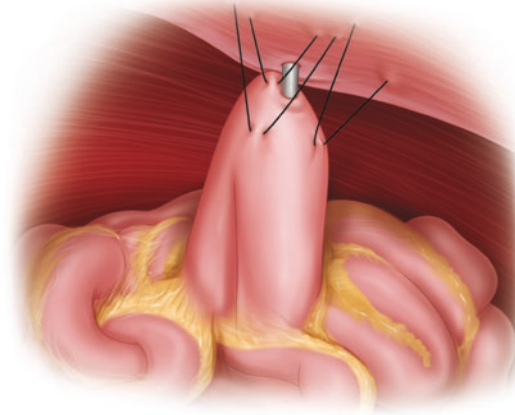


Fig. 14.3 A loop of jejunum is anchored to the abdominal wall with absorbable stitches placed on a diamond shape. A needle is inserted between the stitches to pass a guidewire which will allow placement of a 14F sheath and the feeding jejunostomy

Botox wears off and chronic bile reflux, aspiration and dumping syndrome are prevented.

Next, the bed is leveled for the jejunostomy placement. The colon is lifted superiorly to identify the ligament of Treitz. A proximal loop of jejunum that reaches easily to the abdominal wall of the left mid abdomen is selected for jejunostomy placement. Four absorbable sutures are placed in a diamond pattern on the anti-mesenteric aspect of the bowel, surrounding the planned jejunostomy site. Each suture is brought through the abdominal wall with a Carter-Thompson fascial closure device and secured loosely with hemostats. A Seldinger technique is then used to perform a percutaneous jejunostomy (Fig. 14.3). Care is taken to ensure the tube is intraluminal and not dissecting within the wall of the bowel and is directed antegrade. Once the tube has been inserted, the four anchoring sutures are tied externally within the subcutaneous layer, securing the jejunum to the anterior abdominal wall. Next an anti-torsion stitch is placed about 2 cm distal to the jejunostomy itself. The tube is secured to the skin with non-absorbable sutures. After the jejunostomy is completed, the transverse colon and the omentum are returned to their standard position.

Transhiatal Dissection

The bed is returned to reverse Trendelenburg position to begin the transhiatal dissection of the esophagus. A ½ inch Penrose drain is passed around the distal esophagus, and secured with a locking clip to create a mobile handle. Using the drain to aid in retraction, a transhiatal dissection is performed as high as feasible, about to the level of the inferior pulmonary vein. Periesophageal lymph nodes, including nodes anteriorly along the back of the pericardium should be kept en bloc with the specimen. If a pneumothorax occurs at this point, make the pleural opening wide enough to avoid entrapment of air within the chest and tension physiology. If hemodynamic instability due to pneumothorax is noted several remedies can be employed. Decreasing the intra-abdominal insufflation pressure, increasing the airway pressure and taking the patient out of steep reverse Trendelenburg are useful maneuvers that resolve the problem in most cases. Placement of a chest tube is almost never required.

Creation of the Gastric Conduit

A location on the lesser curve, just cranial to the pylorus is selected to begin tubularization of the conduit. Ensure that the orogastric tube is withdrawn to avoid it being caught in the staple line. Begin dividing the conduit from the specimen, proceeding superiorly toward the fundus. Create a conduit 4–5 cm in width and keep the staple line as straight as possible by stretching the stom-

ach from the tip of the fundus (Figs. 14.4 and 14.5). Stop the staple line approximately 3 cm proximal to the fundus so that the specimen and conduit can later be delivered into the chest together in the proper orientation. Finally, pass the Penrose drain through the hiatus where it will later be retrieved via the chest. Remove the liver retractor, ensure hemostasis and close all port sites in the standard fashion.

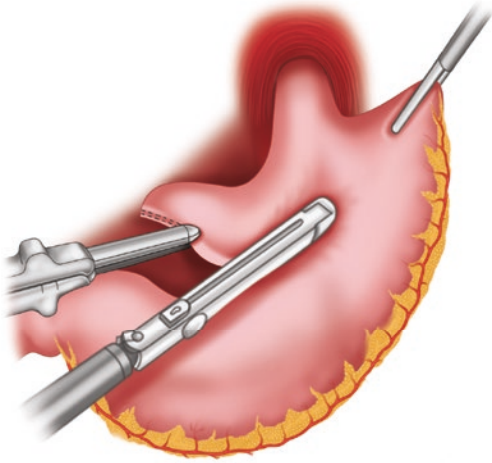


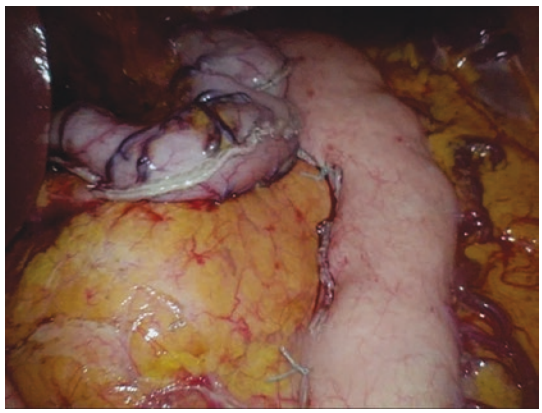
Fig. 14.4 The stomach is stretched at the fundus during tubularization to avoid twisting and folding. Tubularization is started just above the pylorus to allow unfolding of the lesser curvature and adequate conduit length

Positioning for the Thoracic Phase and Port Placement

The patient is positioned in the left lateral decubitus position leaning slightly forward on a bean bag, with an axillary roll and arm support and with the table flexed. At this point anesthesia should switch to single lung ventilation. The chest is entered under direct visualization with a 10 mm optical trocar in the seventh intercostal space in the posterior axillary line. Additional ports are placed as follows: A 10 mm camera port in the ninth intercostal space just posteriorly to the first port, a 10 mm port in the fourth or fifth intercostal space in the mid-axillary line, and a 5 mm port in the seventh intercostal space between the scapula and the spine (Fig. 14.6). Chest insufflation with CO_2 at a pressure of 8 mmHg helps exposure by flattening the diaphragm, collapsing the lungs towards the anterior mediastinum and decreasing movement of the mediastinum.

Thoracoscopic Dissection

The inferior pulmonary ligament is divided and the associated lymph nodes removed. The mediastinal pleura is incised anteriorly to the esophagus, heading superiorly to the level of the azygos vein which is divided using a vascular stapler. Next, the dissection is carried back down to the diaphragm, this time dividing the pleura posterior to the esopha-



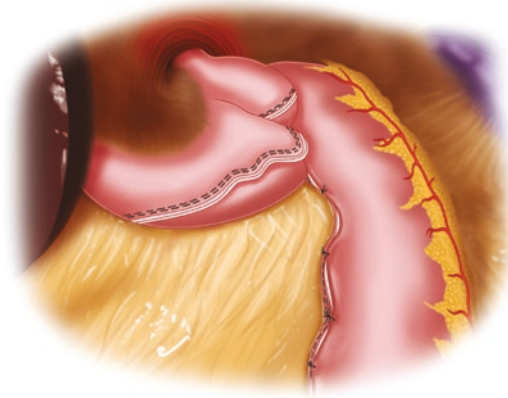


Fig. 14.5 The conduit is not completely divided from the specimen to facilitate transposition in the chest. A few interrupted stitches over the staple line are useful to minimize gastric injury or hematomas during retraction of the stomach

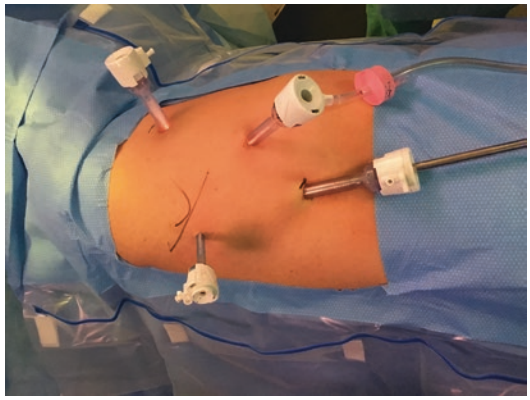


Fig. 14.6 Thoracic port placement

gus. As the dissection is carried inferiorly the transhiatal dissection performed via the abdomen is eventually encountered. Locate the Penrose drain and use this as a retraction handle. Dissect the esophagus completely out of its bed in the mediastinum, proceeding again superiorly toward the level of the azygos vein. The thoracic duct is at particular risk for injury during esophageal mobilization in the chest because of its inconsistent course and the fact that it is often difficult to visualize, especially in obese patients or after neoadjuvant radiation. Injury occurs when dissection strays outside of the periesophageal plane of dissection. Identify and clip lymphatic branches coming from the thoracic duct and arterial branches from the aorta. Prophylactic ligation of the thoracic duct itself has not consistently been shown to reduce postoperative chylothorax, but if injury to the duct or its branches is suspected the duct should be ligated just above the hiatus. Fluorescence imaging may be useful to help delineate the anatomy of the duct to aid in its preservation or ligation, though it is not routinely necessary [11].

Complete the lymphadenectomy by dissecting the subcarinal nodes, again taking care not to injure or devascularize the airway. Avoidance of injury to the airways, including the trachea and both mainstem bronchi, is vital in preventing tracheoesophageal fistula. Exercise caution when using energy devices near the airway, particularly during the subcarinal node dissection. Even minor thermal injury to the airway, often not even visible during the operation, can progress over the course of several days to a full thickness injury and fistula formation. In addition, bronchial artery branches supplying the airway should be preserved to prevent ischemia. Always ensure that the bronchial cuff of the double lumen endotracheal tube is not overinflated, which can put the left mainstem bronchus at increased risk of injury.

Esophagogastric Anastomosis

The dissection of the esophagus is extended beneath the pleura around 2 cm superiorly past where the pleura was divided at the level of the azygos vein. The preserved pleura will act as a buttress for the eventual anastomosis. Divide the esophagus with a linear stapler at the level of the azygos vein, after confirming that the orogastric tube and esophageal temperature probe have been removed. Tension is minimized by placing the anastomosis no higher in the chest than necessary but at least at the level of the azygos vein to avoid redundant gastric conduit in the abdomen which can lead to reflux. Next, the anesthesiologist gently advances an oral anvil for the circular stapler (Orvil, Medtronic, Minneapolis, MN). Grasp the staple line both sides to help guide the tube and keep the staple line horizontal. Once the tip of the tube can be seen, use cautery to create a small opening just above the center of the staple line. Grasp the end of the tube and pull it through as the anesthesiologist guides the anvil over the back of the palate (Fig. 14.7).

The distal esophagus is gently pulled upwards to deliver the specimen and the conduit into the chest. Avoid excess traction and any twisting of the conduit. The staple line of the conduit should be oriented to the patient's right and be totally straight. At this point the conduit can be assessed using fluorescence imaging using a proprietary camera such as the Pinpoint system (Novadaq, Ontario, Canada). The speed of fluorescence appearance and any areas of demarcation can help to identify regions of poor perfusion in the conduit. If a demarcation is seen, mark the area so that the anastomosis can be created caudally where there is preserved perfusion, resecting the poorly perfused portion of the stomach after the anastomosis is performed [11].

Divide the specimen from the conduit using a linear stapler, taking care to maintain an ade-

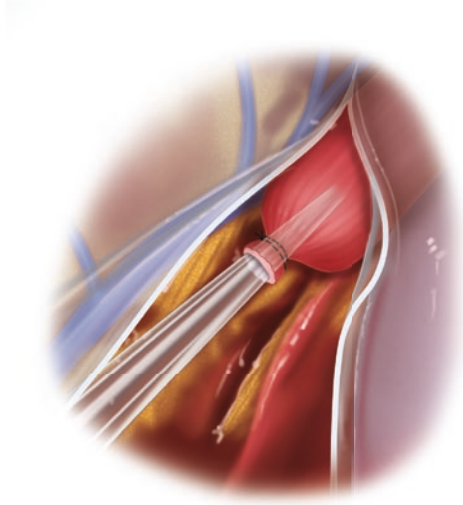


Fig. 14.7 The Orvil is retrieved through an opening in the esophageal stump. It is important to stay as close as possible to the esophageal stump staple line so that this is cut by the circular stapler

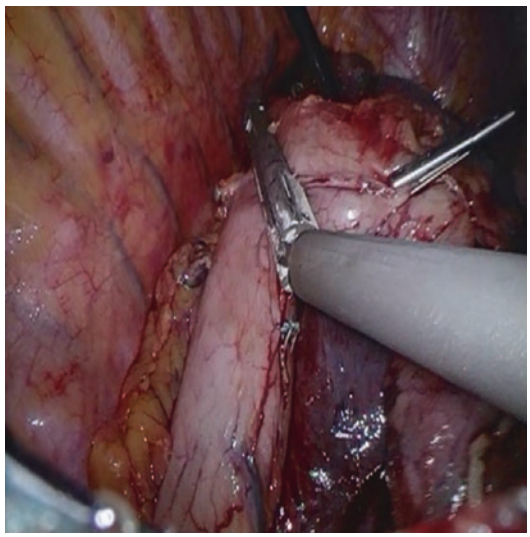


Fig. 14.8 The specimen is retracted towards the anterior mediastinum and the conduit is completely divided making sure the margin at the level of the hiatus is not compromised

quate margin and leave enough room for insertion of the circular stapler to form an end to side esophagogastric anastomosis (Fig. 14.8). The specimen is removed in a retrieval bag and sent for intraoperative assessment of the proximal and distal margins. The anastomosis is performed only after the margins are confirmed to be uninvolved. Grasp the proximal tip of the conduit and open parallel to the staple line with cautery, wide enough to allow insertion of the circular stapler. Insert the stapler and perform the anastomosis in an area of good conduit perfusion with no tension, leaving the greater curvature vessels on the tracheal side of the anastomosis in order to protect the airways in case of leak (Fig. 14.9). After the stapler is removed, transect the opened proximal end of the conduit with a linear stapler, making sure the anastomosis and this gastric staple line are at least 1–2 cm apart to avoid ischemia (Fig. 14.10). At this point the anastomosis is allowed to retract under the superior mediastinal pleura.

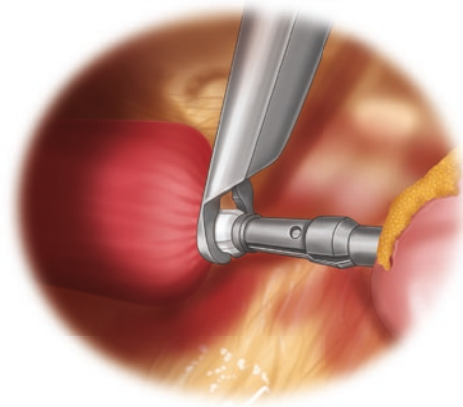


Fig. 14.9 The anastomosis is performed using a special grasper designed for use with the Orvil. The greater curve vessels are positioned against the airway to protect against fistula formation in the case of a leak. The preserved mediastinal pleura which will cover the eventual anastomosis is seen

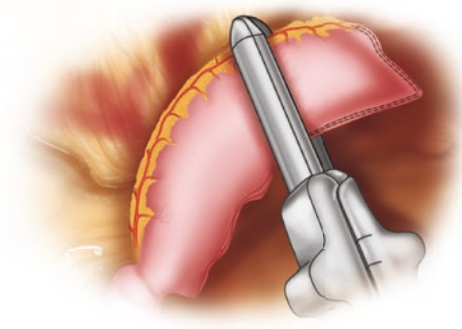


Fig. 14.10 Resection of opened proximal end of the conduit with linear stapler

Tack the conduit to the pleura with absorbable sutures. Buttress the vertical staple line of the conduit with omentum or pericardial fat, separating it from the airway. The anesthesiologist then advances a nasogastric tube under direct vision until the tip is within the distal conduit. Lastly, tack the conduit to the diaphragm at the hiatus with non-absorbable suture to help prevent against paraconduit herniation. Place a single straight 28 Fr chest tube and have the lung re-expanded. Incisions are closed in the standard fashion.

Postoperative Care

Patients should be extubated in the operating room and monitored in the post-anesthetic care unit overnight. Keep the nasogastric tube to suction and keep the patient NPO. Tube feeds can be initiated on post-op day #2 and advanced according to protocol. The nasogastric tube is usually ready to be removed by post-op day #3 or 4, depending on the output and provided the conduit is not distended on X-ray. Contrast esophagram does not reliably identify or rule out a subclinical anastomotic leak and does not need to be routinely performed. The patient can start clear fluids on approximately post-op day #5. The chest tube should be removed once a chyle leak has been ruled out after initiating tube feeds, and if there are no signs of leak, typically by post-op day #3 or 4. Careful attention must be paid to the patient's fluid balance. Most patients benefit from diuresis starting on around post-op day #3, which is often continued up to discharge. Patients should ambulate 1 mile/day and use incentive spirometry at least hourly.

Any unexpected deviation from the clinical course, such as fever, cough or arrhythmia, may signal a more serious complication such as anastomotic leak or pneumonia. These should be investigated appropriately, typically with an IV and oral contrast CT scan of the chest. In the absence of complications most patients are discharged by around post-op day #7. After discharge the patient can slowly advance their diet and tube feeding can be weaned as oral calorie intake improves. The jejunostomy tube can usually be removed at the first follow-up appointment 2 weeks after discharge.

Outcomes

Several studies have compared MIE and open esophagectomy. Biere, et al. randomized 115 patients at five centers to either MIE or open esophagectomy [5]. MIE was superior in terms of blood loss (200 vs 475 mL, $p < 0.001$), length of stay (11 vs 14 days, $p = 0.044$), recurrent laryngeal nerve injury (2 vs 14%, $p = 0.012$), visual analog pain scale (2 vs 3, $p < 0.001$) and several short term quality of life measures, and was inferior only in operative time (329 vs 299 min, $p = 0.002$). Takeuchi, et al. performed a propensity matched comparison of MIE and open esophagectomy in 7030 patients, performed in over 700 Japanese hospitals [4]. MIE was superior in terms of blood loss (442 vs 608 mL, $p < 0.001$), need for >48 h ventilation (8.9 vs 10.9%, $p = 0.006$), rate of atelectasis (3.6 vs 5.1%, $p = 0.002$) and superficial infections (6.7 vs 8.7%, $p = 0.022$). MIE was inferior in terms of operative time (526 vs 461 min, $p < 0.001$), recurrent laryngeal nerve injury (10.3 vs 8.1%, $p = 0.002$) and the need for reoperation (7 vs 5.3%, $p = 0.004$) though there was no difference in anastomotic leak, pneumonia, overall morbidity, or operative and 30 day mortality. Sihag, et al. retrospectively studied the Society of Thoracic Surgeons database to compare MIE and open esophagectomy in 3740 patients [6]. MIE was superior in terms of length of stay (9 vs 10 days, $p < 0.001$), postoperative transfusions (14.1 vs 18.7%, $p = 0.002$) and wound infections (2.3 vs 6.3%, $p < 0.001$) but was inferior in terms of operative time (443 vs 312 min, $p < 0.001$), empyema (4.1 vs 1.8%, $p < 0.001$), need for reoperation (9.5 vs 4.4%, $p < 0.001$), and need for dilation prior to discharge (5.5 vs 1.9%, $p < 0.001$). Key results of these and other studies are summarized in Table 14.1.

Surgical Tips

Abdominal Phase

– The addition of a 5 mm port in the left upper quadrant allows both the primary surgeon and the first assistant to work with two hands, which can facilitate exposure. This is especially useful when less experienced trainees

Table 14.1 Superior operative approach for selected surgical and oncologic outcomes

Outcome	Biere [5]	Takeuchi [4]	Sihag [6]	Tapias [7]	Palazzo [9]
Length of stay	MIE	ND	MIE	MIE	MIE
ICU length of stay/ventilation	ND	MIE	ND	MIE	–
Operative time	OE	OE	OE	ND	–
Blood loss/transfusion	MIE	MIE	MIE	MIE	MIE
Anastomotic leak	ND	ND	ND	ND	ND
Recurrent nerve injury	MIE	OE	–	ND	–
Superficial/wound infection	–	MIE	MIE	–	–
Pneumonia/empyema	–	MIE	OE	ND	MIE
Pain	MIE	–	–	–	–
Need for reoperation	ND	OE	OE	–	–
Margin	ND	–	–	ND	ND
Nodes removed	ND	–	–	ND	MIE
Operative/30 day mortality	ND	ND	ND	ND	ND

MIE minimally invasive esophagectomy-blue, OE open esophagectomy-yellow, ND no difference-grey

are involved, but as expertise is gained, this port can be omitted without compromising the operation.

- Minimize grasping the greater curve of the stomach, which will become the conduit. Plan grasper placement carefully for retraction during each phase of the stomach mobilization, so that the grasper doesn't have to be continually readjusted. Bluntly lift the stomach instead of grasping it when possible.
- Avoid performing transhiatal dissection until late in the abdominal phase. This avoids a pneumothorax early in the case with resulting issues with hypotension. If a pneumothorax does occur it can usually be managed without inserting a chest tube.
- The use of the Carter-Thompson fascial closure device and the Endostitch (Covidien, Dublin, Ireland) greatly facilitates the creation of the jejunostomy, which can be one of the most frustrating parts of the operation when starting out.

Thoracic Phase

- The use of CO_2 insufflation aids exposure and stabilizes the surgical field.
- Locate the previously placed Penrose drain early on after dividing the mediastinal pleura anteriorly and posteriorly. This provides a useful handle to retract the esophagus during dissection.

– Preserving the mediastinal pleura above the azygos vein provides an envelope of pleura to surround the anastomosis and allows anchoring the conduit to combat the effects of gravity when the patient is upright.
– It is often easiest to perform the subcarinal node dissection separately, after the esophagus is completely mobilized.
– Assess the conduit using fluorescence, color and/or Doppler signal. This will help select the ideal location for the anastomosis.

Intraoperative Trouble Shooting

– Hypotension is a common occurrence during the abdominal phase, and is typically related to patient positioning or a pneumothorax. If hypotension occurs, start by taking the patient out of reverse Trendelenburg position. If this solves the problem, gradually reintroduce reverse Trendelenburg to allow the patient time to compensate. If a pneumothorax is suspected, ensure that the pleural opening is extended widely to prevent tension physiology. Decreasing CO_2 insufflation pressure can help in both circumstances. Communicate with the anesthesia team to avoid excess administration of IV fluids, often a reflex reaction to transient hypotension, and which can be associated with cardiac and pulmonary complications postoperatively.
– Ensure that the bronchial cuff of the double lumen tube is not overinflated. If it is, the membranous wall of the left mainstem bronchus can be stretched and prone to injury during esophageal mobilization and subcarinal node dissection.
– When performing the anastomosis, double check that the conduit is not twisted. The staple line should be straight and to the patient's right (up towards the ceiling with the patient in decubitus positioning). The greater curve vessels should lie to the left and are laid to buttress between the conduit and the airway.

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Hybrid Esophagectomy

15

Marco G. Patti, Jason Long,
and Francisco Schlottmann

Our Patient

The patient is a 58 year-old man with a 20-year history of heartburn. During these years he had been treated by his family doctor with H2 blocking agents first, and then with daily proton pump inhibitors. During the last 3 years, he developed progressive regurgitation, particularly at night, when he often woke up with food in his mouth, and coughing. Concerned about these nocturnal events, he was able to convince his doctor to refer him to a gastroenterologist for a full work-up. Eventually these were the results of his tests:

- High-resolution esophageal manometry showed a hypotensive lower esophageal sphincter (LES), ineffective esophageal motility, and a 7 cm hiatal hernia.
- The ambulatory pH monitoring was performed off medications and using a catheter with two antimony sensors that measured acid reflux 5 and 20 cm above the upper border of the manometrically detected LES. The reflux score was 89 in the distal esophagus (normal <14.7) and 12 in the proximal esophagus. The esophageal acid clearance was significantly prolonged.
- The upper endoscopy confirmed the presence of the hiatal hernia. In addition, it showed a 10 cm segment of Barrett's epithelium with an 8 mm nodule located 2 cm above the gastroesophageal junction. Biopsies showed multifocal high-grade dysplasia throughout the entire segment. Endoscopic mucosal resection of the nodule showed an adenocarcinoma extending to the deep margins of resection.
- A PET CT showed no solid organ metastases.

After consultation with both the gastroenterologist and a surgeon, the patient decided to undergo an esophagectomy.

Surgical Technique

The hybrid esophagectomy combines a laparoscopic approach for preparation of the gastric conduit, followed by a right muscle sparing thoracotomy for resection of the esophagus, gastric pull-up, and esophago-gastric anastomosis. Before starting the operation, the anesthesiologist

M. G. Patti (✉)
Department of Surgery, University of North Carolina, Chapel Hill, NC, USA

Department of Medicine, University of North Carolina, Chapel Hill, NC, USA
e-mail: marco_patti@med.unc.edu

J. Long
Department of Surgery, University of North Carolina, Chapel Hill, NC, USA
e-mail: jason_long@med.unc.edu

F. Schlottmann
Department of Surgery, Hospital Alemán of Buenos Aires, University of Buenos Aires, Buenos Aires, Argentina

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places an epidural catheter, a double lumen endotracheal tube, and an arterial catheter.

Laparoscopic Phase

The patient is placed over an inflated beanbag and the legs are extended on stirrups with the knees flexed 20–30°. Pneumatic compressions stockings are used as prophylaxis against deep vein thrombosis. The surgeon stands between the patient's legs, with one assistant on the patient's right side and another on the patient's left side. If the surgeon is right handed, the scrub nurse will stand over the patient's left foot (Fig. 15.1).

Five trocars are used for the operation. Port A is placed in the midline, about 18 cm below the xiphoid process, and it is used for the insertion

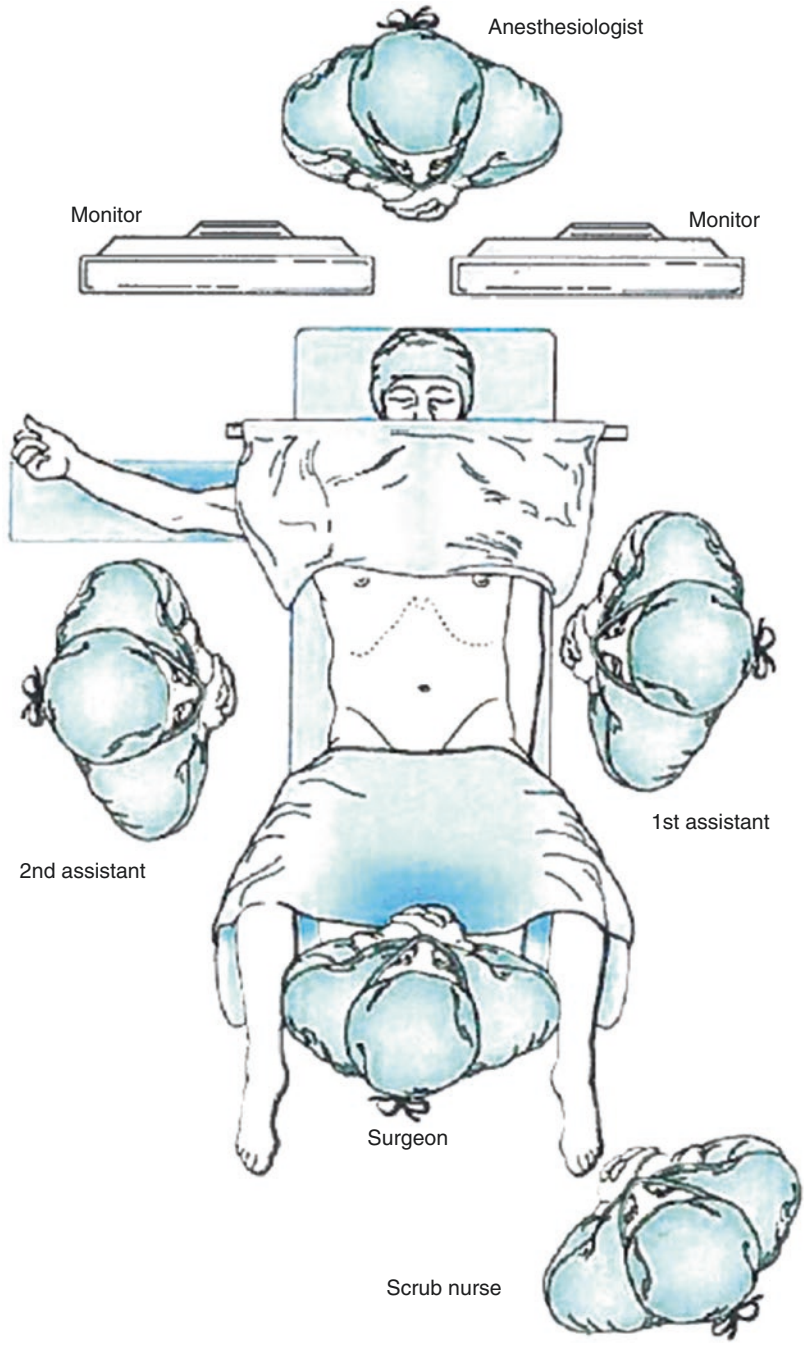


Fig. 15.1 Position of the operating team around the operating table. Reproduced with permission from Atlas of Esophageal Surgery, P. Marco Fisichella, Marco G. Patti editors, Springer

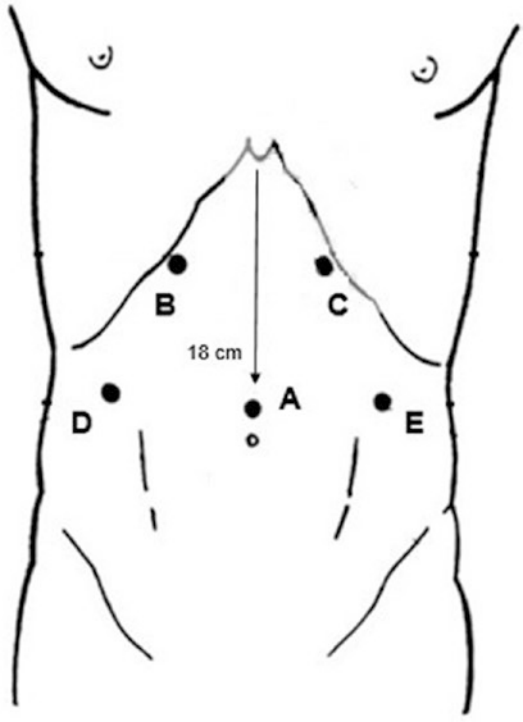


Fig. 15.2 Placement of abdominal ports

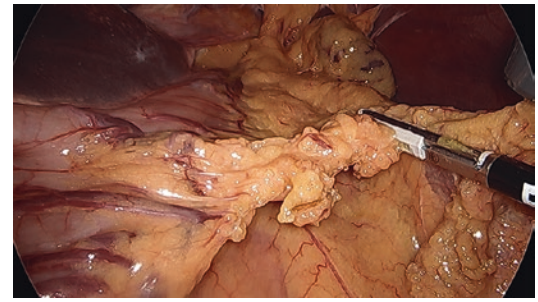


Fig. 15.3 Dissection along the greater curvature of the stomach

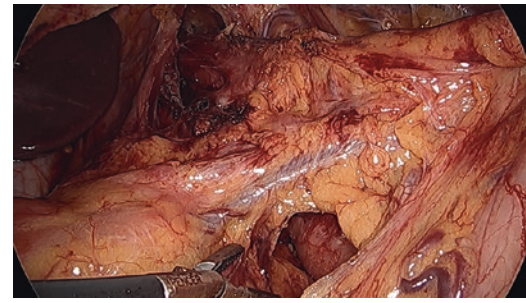
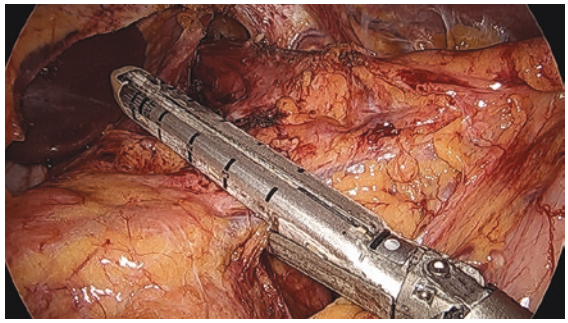


Fig. 15.4 The coronary vein and left gastric artery are dissected all the way to their base

of a 30° scope. Ports B and C are placed about 2 cm below the right and left costal margins (forming an angle of about 120°), and are used for dissection. Port D is placed at the level of port A in the right mid-clavicular line, and it is used for the liver retractor and for a bipolar instrument to open the gastro-colic omentum. Port E is placed at the level of port A in the left mid-clavicular line, and it is used for a Babcock clamp, for insertion of a bipolar instrument to take down the short gastric vessels, and for insertion of a stapling device to transect the coronary vein and the left gastric artery. If a pyloroplasty is performed, an additional port is placed in between ports A and D, usually about 5 cm below them (Fig. 15.2).

The dissection is started by identifying the right gastroepiploic artery and opening the gastro-colic omentum (Fig. 15.3). The dissection is then continued taking down all the short gastric vessels all the way to the left pillar of the crus, which is then separated from the esophagus. The gastro-hepatic ligament is divided respecting the right gastric artery. The esophagus is separated from the right pillar of the crus. If an accessory left hepatic artery originating from the left gastric artery is present, it is divided in between clips. The phrenoesophageal membrane is then divided and dissection of the esophagus is performed in the posterior mediastinum for about 5 cm. A window is created between the esophagus, the left pillar of the crus and the stomach, and a Penrose drain is passed around the esophagus and pushed as high as possible. The drain will help with the thoracic dissection, and it will be retrieved from the chest. The coronary vein and the left gastric artery are dissected all the way to their base in order to retrieve as many lymph nodes as possible, and then are transected using an a laparoscopic stapler with a vascular cartridge, inserted through port E (Figs. 15.4 and 15.5). Upon completion of this step, the blood supply of the stomach is based on the right gastric and right gastroepiploic arteries. Posterior adhesions between the posterior wall



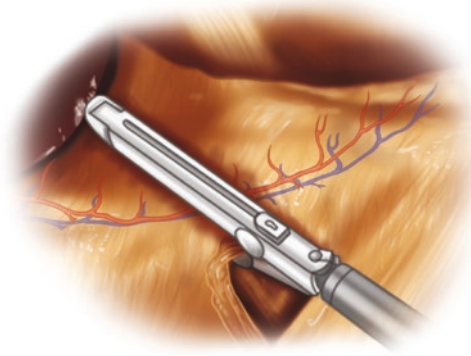


Fig. 15.5 An Endo GIA™ stapler (Covidien, Minneapolis MN) with a 45-mm vascular cartridge is used for the transection of the coronary vein and left gastric artery

of the stomach and the pancreas are then taken down using the cautery. We do not perform a Kocher maneuver.

In the past, we routinely performed a laparoscopic pyloroplasty. During the last years we have omitted this step: we build a gastric tube rather than using the entire stomach and, in case of delayed gastric emptying, we inject endoscopically botulinum toxin into the pylorus.

After a final inspection, the trocars are removed, the trocars sites are closed, local anesthesia is injected, and sterile dressings are applied.

Thoracic Phase

After the laparoscopic component of the operation is completed, the patient is positioned in a left lateral decubitus. The chest is entered through a muscle sparing thoracotomy in the fifth intercostal space (Fig. 15.6). Resection of a 1.5-cm long segment of the posterior portion of the sixth rib facilitates the positioning of a retractor to achieve the optimal exposure of the surgical field. After ruling out the presence of metastases, the inferior pulmonary ligament is divided, and the pleura is opened above and below the azygos vein. An Endo-GIA linear stapler with a vascular cartridge is used to divide the azygos vein (Fig. 15.7). Then, the dissection of the esophagus is performed beginning about 3 cm above the azygos vein all

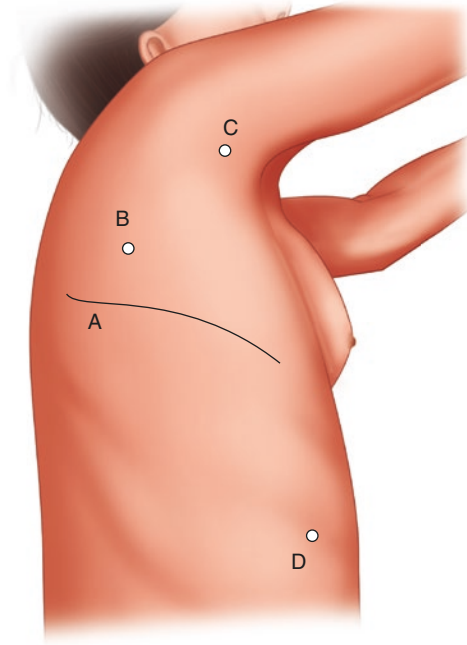


Fig. 15.6 Position of patient for right thoracotomy. (*A*) Thoracotomy in fifth intercostal space. (*B*) Inferior angle of scapula. (*C*) Posterior axillary line. (*D*) Port for ligasure dissection and chest tube in eighth or nineth intercostal space, anterior to anterior iliac spine

the way down to the gastroesophageal junction, thus joining the mediastinal dissection previously performed by laparoscopy (Fig. 15.8). The stomach is pulled up into the chest, a window is opened along the lesser curvature about 8 cm below the gastroesophageal junction, and transection of the

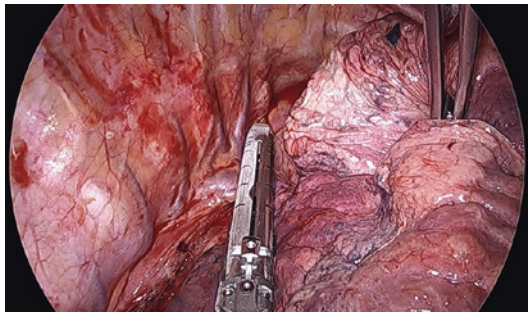


Fig. 15.7 An Endo GIA™ stapler (Covidien, Minneapolis MN) with a 45-mm vascular cartridge is used to divide the azygos vein

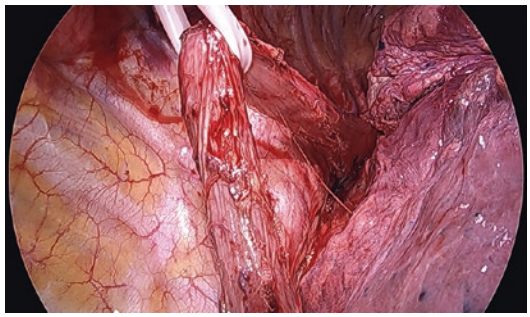


Fig. 15.8 Dissection of the thoracic esophagus

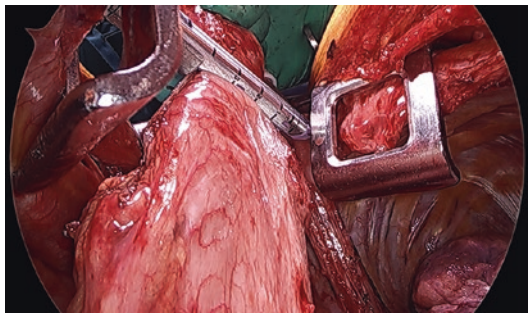


Fig. 15.9 Creation of the gastric conduit in the chest

upper portion of the stomach along the lesser curvature is performed by using a Endo-GIA stapler (Fig. 15.9). After the gastric conduit is created, 5 mg of indocyanine green (ICG) are injected intravenously as a bolus in order to assess the adequate perfusion of the conduit with fluorescence imaging (Fig. 15.10).

The esophagus is placed over the anterior wall of the stomach, clamped with a Satinsky clamp to avoid separation of the mucosa from the muscular layers, and transected about 3 cm above the azygos vein (Fig. 15.11). Full-thickness 3-0 silk stay sutures are placed to keep the posterior wall of the esophagus aligned with the anterior wall of the gastric fundus. Sliding of the esophageal mucosa when the stapler is inserted is avoided by placing 3-0 silk stay sutures at the four edges of the esophageal opening that keep together the mucosa with the other layers of the esophageal wall (Fig. 15.12). The anterior wall of the stomach is opened just distal to the esophageal transection line and interrupted 3-0 silk stiches are used to fix the gastrotomy to the posterior wall of the esophagus. After inserting the thinner branch of a 45 mm Endo-GIA stapler into the stomach and the thicker branch into the esophagus, the stapler is fired, thus constructing a 4 cm long side-to-side anastomosis between the posterior wall of the esophagus and the anterior wall of the stomach (Fig. 15.13). A nasogastric tube is passed under direct vision into the stomach so that the tip is above the diaphragm. The closure of the anterior aspect of the anastomosis is obtained in two layers: an inner layer of running 3-0 absorbable braided suture, followed by an outer layer of interrupted 3-0 silk sutures (Fig. 15.14).

One chest tube is placed, and after direct visual evaluation of the expansion of the lung, the thoracotomy is closed in layers.

Postoperative Course

The patient was extubated in the operating room, spent one night in the intensive care unit, and then was transferred to a regular floor bed. Liquids were started on post-operative day 4 and a soft diet was initiated on post-operative day 6, when the chest tube was removed. The patient was discharged home on postoperative day 8.

Comments

Recent years have seen a decrease in the mortality of esophageal resection for cancer. Patient selection and better perioperative care have

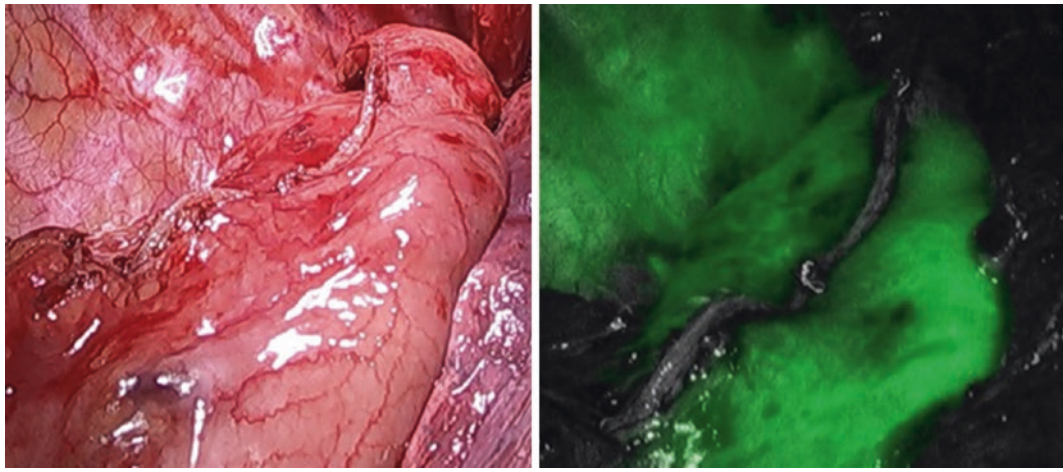


Fig. 15.10 Perfusion assessment of the gastric conduit with ICG fluorescence imaging (Stryker Endoscopy, San Jose, CA)

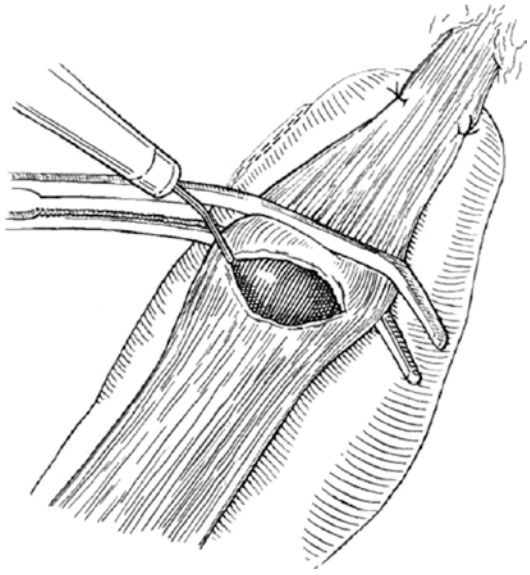


Fig. 15.11 Transection of the esophagus with electrocautery. The Satinsky clamp is key to avoid separating the mucosa from the muscle layers. Reproduced with permission from Atlas of Esophageal Surgery, P. Marco Fisichella, Marco G. Patti editors, Springer

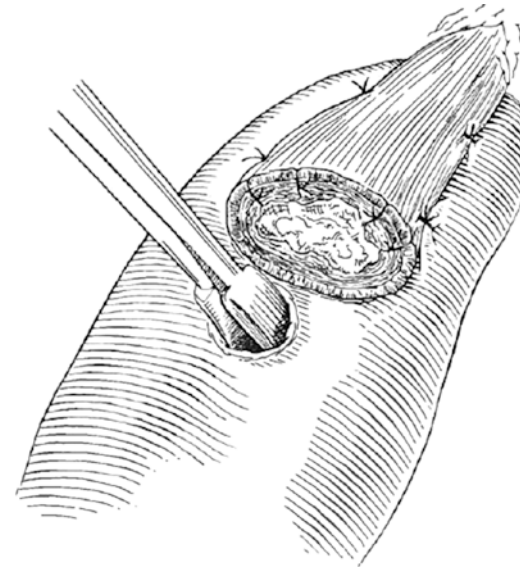


Fig. 15.12 Placement of stay sutures laterally and anteriorly in the esophagus to avoid sliding of the mucosa when the stapler is inserted. Reproduced with permission from Atlas of Esophageal Surgery, P. Marco Fisichella, Marco G. Patti editors, Springer

contributed to this improvement in the results, but a lot of this progress is clearly due to the introduction of minimally invasive techniques for esophageal resection—minimally invasive esophagectomy (MIE) [1]. The approach, laparoscopic and/or thoracoscopic, is based on the idea that, similar to other operations for esophageal disorders such as a laparoscopic fundoplication or Heller myotomy, patients have less postoperative pain, less complications, and a faster return to daily activities. Nagpal et al. [2] published in 2010 a meta-analysis of retrospective studies comparing a MIE to open esophagectomy and showed that the MIE (total

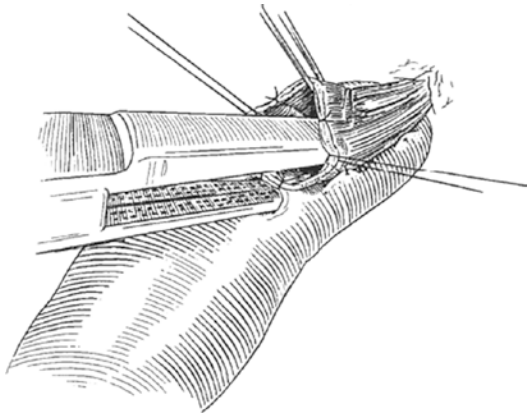


Fig. 15.13 Insertion of the stapler, with the thinner arm into the stomach and the thicker arm into the esophagus. Reproduced with permission from Atlas of Esophageal Surgery, P. Marco Fisichella, Marco G. Patti editors, Springer

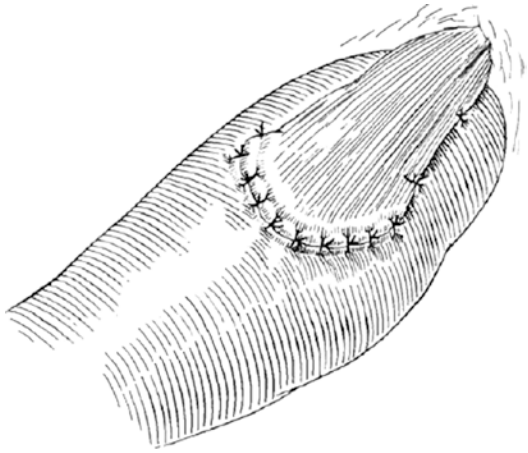


Fig. 15.14 Closure of the anterior aspect of the anastomosis. Reproduced with permission from Atlas of Esophageal Surgery, P. Marco Fisichella, Marco G. Patti editors, Springer

or hybrid) was associated to decreased blood loss, decreased time in the ICU, less complications (including pulmonary complications), and shorter hospital stay. Two recent prospective and randomized trials, comparing the open esophagectomy with the MIE (either total or with laparoscopic gastric mobilization followed by thoracotomy) have confirmed that the minimally invasive approach determines a decrease in complications, particularly major pulmonary complications [3, 4].

A very important study was recently published by Messager et al. [5] on behalf of the FREGAT working group. For this study, they used the French Medical Information System, a French National Health Service prospective database that covers all hospitals in France. Between 2010 and 2012, 3009 patients underwent an esophageal resection with gastric pull-up—2346 with a laparotomy and a thoracotomy (open group) and 663 with laparoscopic gastric mobilization (LGM) followed by a thoracotomy. After propensity score matching, the 30-day post-operative mortality (POM) was significantly lower in the LGM group at 30 days (3.3% vs 5.9%). In the matched population, multivariable analysis identified LGM as the only variable responsible for this 40% decrease in POM. These data suggest that this approach should be widely implemented in order to decrease the morbidity and mortality associated with an esophageal resection.

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Colonic Interposition After Esophagectomy

16

Michele Valmasoni and Stefano Merigliano

Introduction

Colon was historically the first bowel segment to be used as a substitute for the esophagus; the first colonic interposition after esophagectomy was successfully performed by Von Hacker in 1914. After the 1960s, however, the stomach replaced the colon as the conduit of choice because its vascularization is more reliable, the functional results are better, and the substitution is technically easier requiring only one anastomosis. Today, after esophagectomy for cancer, the colon is used only when the stomach is not available.

Indications

Colonic interposition is indicated whenever the stomach is not available because of history of gastric surgery, the necessity of extended gastric resection for oncological reasons, vascular impairment or other gastric pathology such as caustic burns. Colon is the bowel of choice after previous gastric conduit failure.

Contraindications to the use of colon include history of colon surgery, the presence of significant colon pathology (e.g. diverticula and tumors) or alteration to its vascular integrity.

Preoperative Evaluation

The patient's preparation includes oncological staging and typical preoperative studies necessary for major surgery (with particular attention to the presence of diabetes, cardio-vascular and pulmonary pathology). The need to perform a thoracotomy for esophagectomy and reconstruction at the same time requires a careful assessment of the functional respiratory reserve. Nutrition is very important and if the oncological timing allows it, it is preferable to obtain the best possible nutritional status before proceeding with surgery.

The preoperative evaluation of the colon is fundamental and should be performed with a contrast enema or alternatively with a colon-computed tomography to rule out the presence of colon pathology and to evaluate the length of the colon. We do not perform routinely endoscopy and angiographic study is performed only in the presence of particular indications (e.g. history of vascular pathology, symptoms suggestive of intestinal vascular insufficiency, previous abdominal surgery).

M. Valmasoni
University of Padova School of Medicine,
Padova, Italy
e-mail: Michele.valmasoni@unipd.it

S. Merigliano (✉)
Department of Surgery, University of Padova School of Medicine, Padova, Italy
e-mail: stefano.merigliano@unipd.it

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Patient Position

If esophagectomy is required, a right thoracotomy is performed in left lateral decubitus. We use the same position even if the resection is performed with minimally invasive technique.

For reconstruction, the patient is placed on the operating bed in a supine position, with legs closed and the arms along the body. The neck should be extended as much as possible, eventually using a roller under the shoulders to accentuate the extension of the head. The head must then be rotated to the right to allow a clear left cervical operating field.

The preparation of the surgical field goes from the jaw to the pubis; the cervical field can be temporarily protected during abdominal step with a sterile drape. It is, however, important to have contemporary access to the two anatomical districts (the abdomen and the neck).

Preparation of the Left Colon

A median xipho-pubic incision allows an easy access to the abdominal cavity and an abdominal retractor allows a correct exposure of the field.

Initial exploration of the peritoneal cavity: any adhesions are lysed very carefully, avoiding injuries to the colon and its mesentery. If, at the initial evaluation, the residual stomach (when present) is sufficient for a distal colon-gastric anastomosis, it is important to pay attention to preserve the gastro-epiploic arch. If the remaining stomach is not sufficient, it is better to complete the gastrectomy.

The greater omentum (if present) is moved upwards and the gastro-colic ligament is sectioned along the whole transverse colon in order to access the transverse mesocolon. In this phase, if the vascularization of the omentum is not satisfactory it is better to remove it, otherwise, we suggest to preserve it, because it could be useful for wrapping the intra-abdominal anastomoses.

The colon is then completely mobilized, releasing and lowering the splenic and the hepatic flexures completely and continuing the dissection to the left until the colon-sigmoid junction, and to the right until the cecum. Particular attention should be paid in respecting the anatomical plane identified by the Gerota fascia in the left and right parietal-colic grooves, to avoid entering the mesocolon with the risk of damage to the vasculature or vice versa to open the renal capsule.

When the colon is completely mobilized, its mesentery is tensioned with a cautious maneuver by pulling the colon vertically so as to be able to evaluate the whole vascular anatomy. The use of trans illumination makes it easy to visualize vasculature in most cases (Fig. 16.1).

The left, middle and right colic vessels, as well as marginal colic vessels, must be identified with certainty; their integrity must be checked (paying attention to the Griffiths point) and we recommend checking the anatomy of the sigmoid vessels too (Fig. 16.2).

At this point, it is necessary to measure the colon segment necessary for the reconstruction. We use a large thread or umbilical tape, starting to measure from the origin of the left colic vessels, following the marginal arcade (and not the colon), passing the middle colic vessels and beyond to obtain a sufficient length (Fig. 16.3). During this measurement it is important to consider the transposition pathway, because the

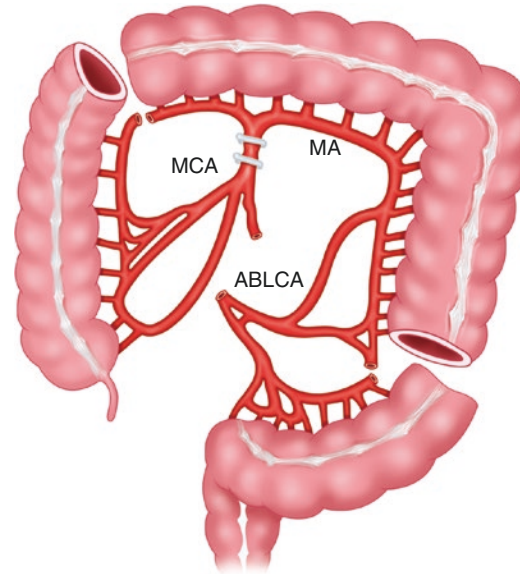

Fig. 16.1 Vascular anatomy of the left colon. *MCA* middle colic artery, *MA* marginal artery, *ABLCA* ascending branch of left colic artery (Drawing by Gonzalo Etchepareborda)

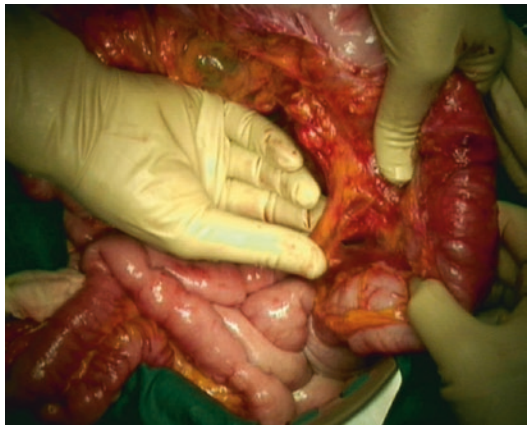

Fig. 16.2 Checking the left colic vessels, after complete colon mobilization

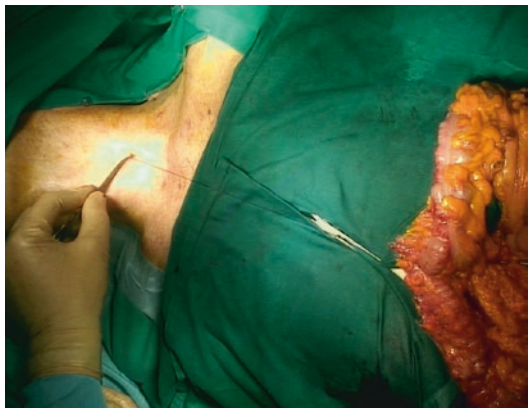

Fig. 16.3 Measuring the needed conduit length from the left colic pedicle to the neck

retrosternal and subcutaneous routes are longer than the posterior mediastinal path.

Once the necessary length has been identified, the mesocolon is opened near the middle colic vessels and the marginal arch, at the identified section point. Before proceeding to the ligation of the vessels, it is necessary to verify the effectiveness of the residual vascularization by placing vascular clamps at the base of the medium colic pedicle (carefully preserving the V-shaped right-left bifurcation) and the marginal arch near the section point. After a few minutes, we proceed to a digital evaluation of the arterial flow and a visual evaluation of the venous outflow; some authors use a Doppler probe for added security (Figs. 16.4 and 16.5).

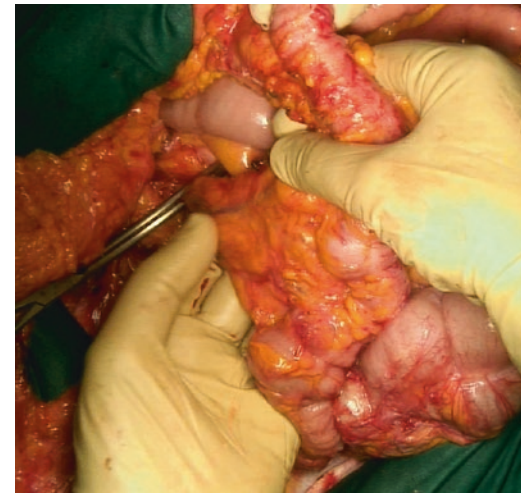

Fig. 16.4 After closing with a clamp the base of the middle colic pedicle and the marginal arch coming from the right, it is important to check if the vascularization from the left colic vessels is valid

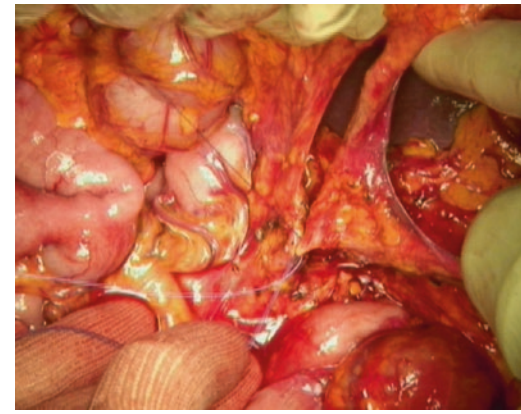

Fig. 16.5 Ligation of the middle colic artery, paying attention to preserve the V-shape left-right bifurcation

When the medium colic vessels and the marginal arch are ligated, the colon is sectioned with a linear stapler; we always prefer to secure the staple line with some hand stitches (Figs. 16.6 and 16.7).

Cervicotomy

A left cervical incision is carried out. It needs to be sufficiently wide, to allow a good vision and an easy mobilization of the esophagus or

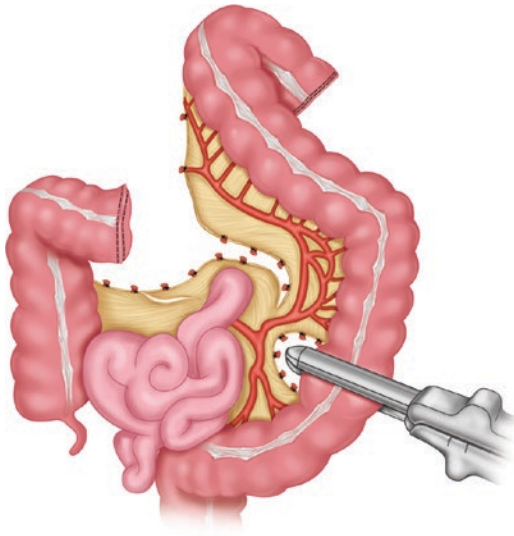

Fig. 16.6 Division of the colon with a linear stapler (Drawing by Gonzalo Etchepareborda)

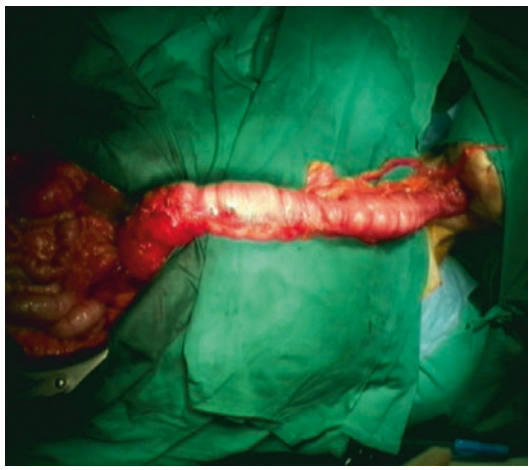

Fig. 16.7 The isolated colonic conduit ready to be transposed to the neck

of the esophageal stump that had been stitched to the skin in a terminal esophagostomy (the cervical esophageal segment has to be maintained as long as possible during the esophagectomy).

If the esophagus was mobilized in the thorax during the same operation, we fix a large sponge or tube to the abdominal esophagus in order to bring the sponge along the posterior mediastinal pathway while recovering the esophagus through the cervicotomy. We prefer to fix the colon to the sponge and not to the esophagus for transposition, because of the risk of esophageal rupture during the pull-up.

If the posterior mediastinal pathway is not available, we proceed to the incision of the deep cervical fascia to gain access to the retrosternal space. We remove the sternal head of the left clavicle, to ensure a sufficient passage of the colon while avoiding compression, which can cause local ischemia. In our experience, it is only rarely necessary to perform a sternal split.

Colon Conduit Pull-Up

Posterior Mediastinum Route

This way is anatomically preferable, but not always possible. If the esophagectomy was performed with a previous surgery, mediastinal adhesions render this path unusable.

Before proceeding to colon transposition it is necessary to isolate the diaphragmatic crus to make it wide enough to allow an easy passage of the colon. If necessary, a partial section of the right diaphragmatic pillar can help, taking care not to enlarge the hiatus too much to avoid the onset of visceral hernias.

The colonic segment is wrapped with a sterile plastic bag of adequate length (for example the one used to cover the laparoscopic camera), to guarantee vascular protection during the pull-up, and then fixed to the sponge previously pulled in the posterior mediastinum. With a careful traction of the sponge from the neck, the colon is pulled up, helping the trans-diaphragmatic passage with the hands, until a sufficient portion of the colon reaches the left lateral cervical space. Once the plastic bag has been removed from the neck, the esophagus is dissected to measure for the anastomosis.

The esophago-colic, termino-lateral anastomosis is hand sewn with two semi-continuous 4/0 or 3/0 polydioxanone (PDS) sutures and a second layer of single stitches. Once the posterior wall of the anastomosis has been completed, a nasogastric tube is accompanied through the anastomosis and pushed into the colonic conduit.

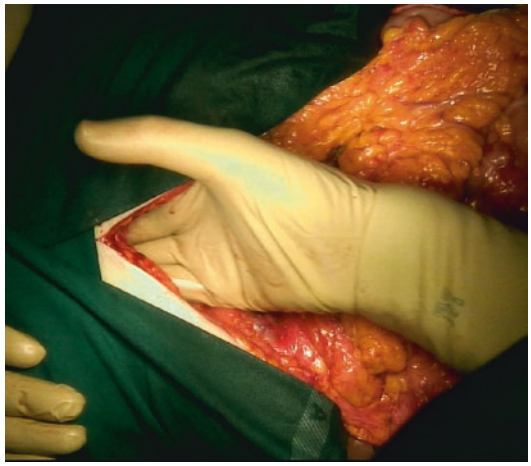

Fig. 16.8 Blunt hand dissection to prepare the retrosternal route

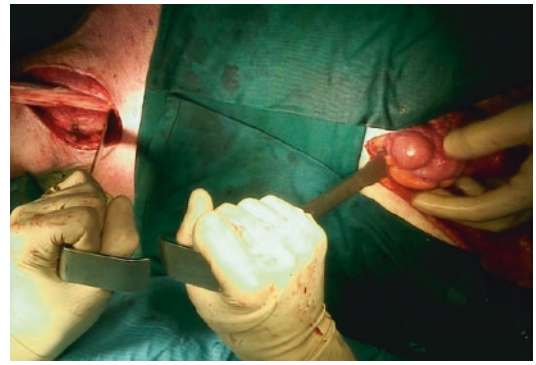

Fig. 16.9 Colon pull-up with a sponge trough the retrosternal route

Retrosternal Route

Before pulling the colonic conduit to the neck trough the retrosternal route, it is necessary to remove the xiphoid process and detach the medial insertions of the diaphragm in order to access the retrosternal space; then, with blunt hand dissection, a retrosternal tunnel is prepared up to the neck, avoiding if possible opening the pleurae (Fig. 16.8). At this stage, it is important that hemostasis is satisfactory before proceeding because it can be difficult to stop bleeding after transposition of the colon. Remember to close the diaphragmatic hiatus to avoid visceral hernias.

The colonic segment is then accompanied through the retrosternal pathway with a long ringed forceps and recovered at the neck to perform the anastomosis (Fig. 16.9).

Subcutaneous Route

The subcutaneous route remains the last chance when the retrosternal pathway is not available, for example for previous sternotomy or irradiation. The removal of the xiphoid process is particularly important to avoid trauma to the colon. The subcutaneous tunnel must be large enough to allow an agile passage of the conduit without compressing it but at the same time not too large to prevent redundancy. Sometimes it is necessary to stage the placement of an expander if the skin is not sufficiently compliant.

Abdominal Anastomoses

After the cervical esophago-colic anastomosis is completed, we verify that the colonic conduit is rectilinear and there is no traction on the anastomosis. Then, the intra-abdominal anastomoses are performed.

The transposed colon must be interrupted in the abdomen to have two sufficiently long portions to perform the proximal anastomosis (colon-gastric or colon-jejunal) and the distal colon-colic anastomosis. Particular care must be taken to isolate the needed colon tract, by interrupting the vasa recta for a sufficient length while preserving the marginal arch scrupulously. We recommend to always remove a small portion of the isolated colon to avoid ischemia of the anastomoses.

If a suitable gastric residue is present, a termino-lateral colon-gastric anastomosis can be performed on the posterior surface of the stomach (hand sewn or with a circular stapler, introduced through a gastrotomy, or semi-mechanical with a linear stapler).

In the absence of a gastric stump, it is necessary to perform a termino-lateral colon-jejunal anastomosis on a Roux-en-Y jejunal loop. This second option allows easier reconstruction and guarantees greater control over bile reflux.

Before performing the proximal anastomosis, the nasogastric tube previously positioned in the colonic conduit is always positioned through this anastomosis.

The colon continuity is then reestablished with colon-colic anastomosis (termino-terminal or latero-lateral) laid in front of the colon-jejunal anastomosis. Our preference for these anastomoses is to perform them with two semi-continuous double layers sutures (Fig. 16.10).

We recommend to always perform a nutritional jejunostomy.

Right Colon: Technical Differences

The dissection of the colon occurs in a similar way to that described for the left colon; in this case, however, it is necessary a sufficient mobilization of the cecum and the last ileal tract. The ileocolic, right colic, and ileal vessels should be exposed and clamped with vascular clamps to verify that the flow of the middle colic vessels is adequate (Fig. 16.11).

The measurement of the necessary colon length takes place as already described, starting from the middle colic pedicle. After ligation of the ileocolic and right colic vessels, and if necessary ileal vessels, the colon is transected from the last ileal tract to the measured length. An appendectomy is always performed. The colonic conduit is transposed to the neck as already described (Fig. 16.12).

An end-to-end or end-to-side esophagus-ileal anastomosis is performed with semi-continuous

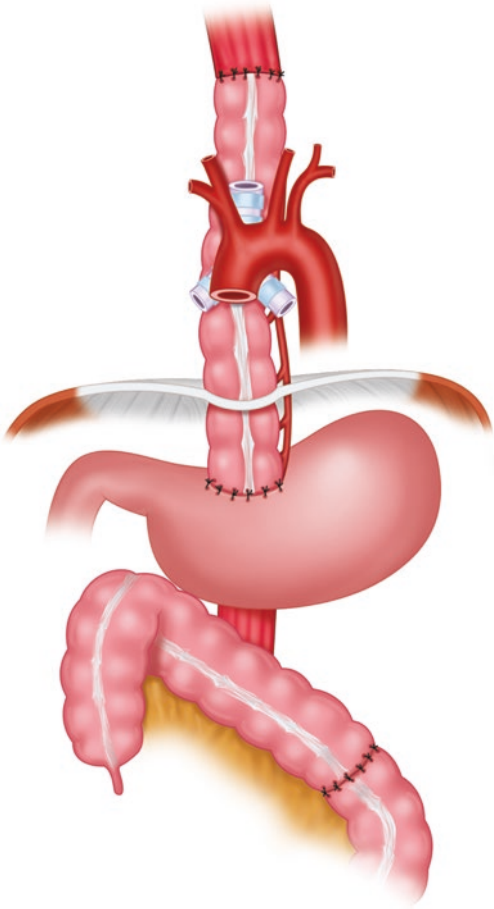

Fig. 16.10 Status after using the left colon for colonic interposition (Drawing by Gonzalo Etchepareborda)

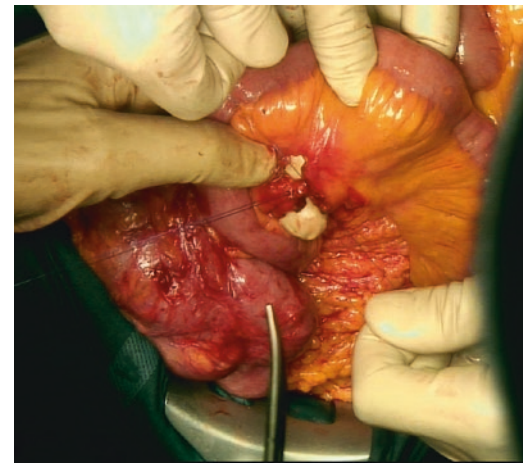

Fig. 16.11 Right colonic conduit preparation: isolation of the last ileal tract

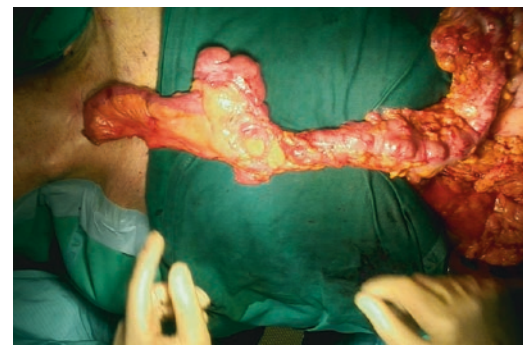

Fig. 16.12 The ileo-colic conduit ready to be transposed

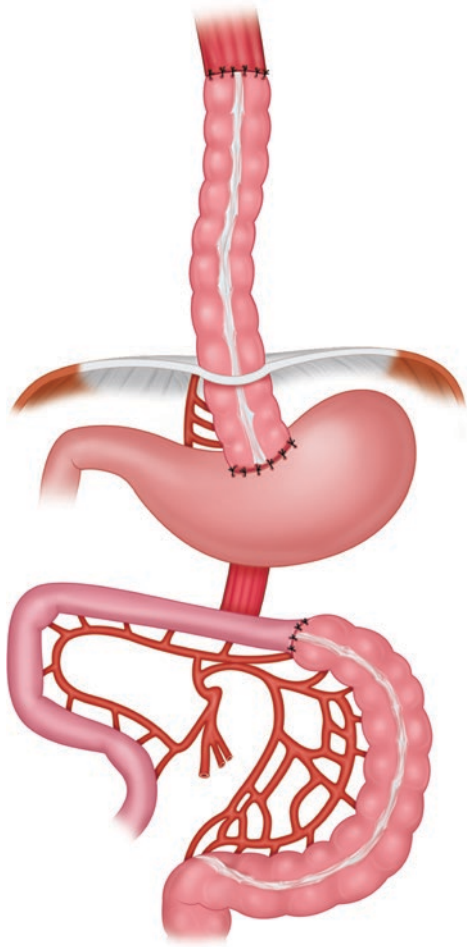

Fig. 16.13 Status after using the right colon for colonic interposition (Drawing by Gonzalo Etchepareborda)

and double-layered 4/0 or 3/0 absorbable monofilament sutures.

Abdominal anastomoses are performed in a similar way to the previous description, with the distal one being an ileo-colic anastomosis (Fig. 16.13).

Postoperative Care

In the early post-operative days, it is important to maintain adequate volume (avoiding fluid overload) and blood pressure, possibly without using vasoconstrictors medications, to avoid the reduction of the microcirculation and the risk of anastomotic ischemia.

We consider early extubation to be important; as well as the mobilization of the patient and an effective use of incentive spirometer. For this reason, postoperative pain control must be optimal.

We maintain the nasogastric tube until the contrast swallow or endoscopic check of the anastomosis, which usually occurs in 7–8 days. The patient then gradually resumes oral feeding while tapering nutritional intake through the jejunostomy.

Outcomes

Results reported in the literature are largely variable, with 0–15% leaks rate, 0–10% conduit necrosis rate, and 0–16% postoperative mortality rate. Risk of leakage has been reported to be higher in patients who underwent chemoradiation [1–11].

Anastomotic leaks can be treated conservatively if promptly diagnosed, if the colon is not ischemic at endoscopy, and if the risk of sepsis is controlled. We suggest to open the cervical incision and drain the leak externally to avoid mediastinitis.

The most severe complication is represented by the necrosis of the colonic conduit; this event often requires immediate surgery, trying to save as much bowel as possible for a future reconstruction. In this case, the prevention of sepsis and adequate nutrition are critical for patient survival.

Dysphagia, reflux, and dumping syndrome may be common in the post-operative period, but these symptoms usually resolve within a few months without specific therapies.

Anastomotic stenosis is described in 0–40% of cases and often can be treated successfully with endoscopic dilations; only a low percentage of cases require re-operation.

In the long run, colonic kinking can occur because of relaxation and redundancy (0–40% of cases in the literature). We believe that there is an

indication to surgery only in the presence of symptoms that have an impact on the quality of life, since corrective surgery is not easy and potentially dangerous for the survival of the colonic conduit.

With regard to the long-term quality of life, the results are very satisfactory, and in some ways superior to gastric transposition, since usually there are no problems related to acid or biliary reflux [12, 13].

Surgical Tips

- When sectioning the esophagus, we perform a knife section of the esophageal muscular layers to obtain a longer mucosal cylinder useful for an easier anastomosis.
- After performing the termino-lateral esophago-colon anastomosis in the neck, sometimes it is useful to approximate the terminal end of the colonic conduit to the esophagus, with some stitches, to avoid the formation of a "cul de sac" that can impair deglutition.
- We recommend resection of the clavicular head even if the passage seems to be large enough when using the retrosternal route.
- Pay particular attention to preserve the V-shaped left-right bifurcation of the middle colic vessels; if necessary perform a tangential resection of the superior mesenteric vessels.
- If the colon conduit vascularization is dubious after the pull-up (congested mucosa, swelling) perform only half of the esophago-colon anastomosis and a temporary cutaneous stoma to check the colonic trophism.
- Some stitches between the colon conduit and the diaphragm crus can help to reduce redundancy, but they have to be placed after the esophago-colon anastomosis have been performed to avoid tension to the anastomosis.

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17 Perioperative Care and Management of Post-Operative Complications

Andrew R. Brownlee and Mark K. Ferguson

Introduction

Esophageal resection has a high postoperative complication rate. This is due, in part, to the inherent comorbid conditions of esophageal malignancy, the morbidity of the operation itself, and a lack of reliable metrics to evaluate a patient's fitness for surgery. For these reasons, there is great emphasis on identifying appropriate candidates for resection, implementing perioperative care plans that are directed at predetermined postoperative goals (e.g. nutritional intake, physical activity, pain management), and focus on minimizing perioperative morbidity and mortality.

Enhanced recovery after surgery (ERAS) programs have benefits in reducing morbidity, cost of hospitalization, and length of stay [1–5]. In patients undergoing esophageal surgery this approach is feasible and safe [6].

A. R. Brownlee · M. K. Ferguson (✉)
The University of Chicago, Chicago, IL, USA
e-mail: Andrew.Brownlee@uchospitals.edu; mferguso@bsd.uchicago.edu

Preoperative Management

Patient Education

The participation of the patient in the entire perioperative process is increasingly important after esophageal surgery. It is incumbent on the surgeon to ensure that patients and their support groups are versed on their essential role in recovery. In the case of esophagectomy for cancer, a brief surgical consultation falls short of appropriately informing a patient of what the operation entails, their role in their own preparation and recovery, and the goals that should be achieved in each stage of the preparation and recovery process. It is essential to start the education process early utilizing a multimodality approach with a unified coherent message, tailoring education to the patient and family and confirming throughout the process that the message is understood. Examples of materials that are useful in this process include printed handouts, question and answer sessions, consultation with esophageal cancer survivors, and videos about the perioperative experience.

Smoking Cessation

Cigarette smokers have an increased risk of pulmonary and wound healing complications, which are mitigated in part by smoking cessation [7, 8].

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Although the required duration of abstinence from smoking to achieve a reduction in complications is not established, greater than 8 weeks is preferable [7–9]. A meta-analysis of randomized controlled trials demonstrated a 41% reduction in both total and pulmonary complications for past smokers compared to current smokers. Each week of cessation increased the magnitude of the effect by 19% [8]. Smoking cessation is best achieved with the combination of behavioral intervention (clinician consultation and continued intervention with support groups or toll-free number support) and medication including nicotine replacement therapy, and should be done in conjunction with the patient's primary care team.

Exercise

Pre- and postoperative exercise regimens reduce morbidity, postoperative pain, and hospital stay after esophageal surgery [10, 11]. Although the regimens used in these studies are heterogeneous, they demonstrate that both pre-and postoperative pulmonary exercises such as incentive spirometry and walking therapy are effective and easily implemented, with goals that enable measurement of progress.

Assessment of Risk for Postoperative Nausea and Vomiting

Postoperative nausea and vomiting (PONV) in esophagectomy patients can delay oral intake and ambulation and increase the risk of aspiration. Identification of patients at risk is accomplished through routine preoperative screening. The Apfel simplified score is a useful quick screen for PONV which assigns a single point to female gender, patients with a history of PONV or motion sickness, non-smoking status, and predicted postoperative opioid use (Table 17.1) [12]. Patients with an Apfel score ≥2 have a greater than 39% chance of postoperative nausea and vomiting and should be considered for prophylaxis, such as the application of a scopalamine patch in the preoperative holding area [12]. The use of low dose propofol (<20 mcg/kg/min) and intraoperative ondansetron reduce PONV and should be considered for all patients in the absence of a contraindication [13].

Table 17.1 Apfel risk scoring system for postoperative nausea and vomiting (PONV)

Apfel score	Risk of PONV (%)
0	10
1	21
2	39
3	61
4	79

A point is assigned for female gender, a history of PONV or motion sickness, non-smoking status, and predicted postoperative opioid use; the sum is the Apfel score [12]

Table 17.2 Incidence of esophageal complications among high volume centers internationally [14]

Complication category	*Incidence (%)*
Pulmonary	27.8
Gastrointestinal	22.4
Cardiac	16.8
Infection	14.2
Neurologic/psychiatric	9.4
Urologic	8.3
Thromboembolic	5.1
Wound/diaphragm	2.9
Other	6.8
Frequent individual complications	*Incidence (%)*
Pneumonia	14.6
Atrial dysrhythmias	14.5
Anastomotic leak	11.4
Chyle leak	4.7
Recurrent laryngeal nerve injury	4.2
Conduit necrosis	1.3

Predictors of Perioperative Complications

Postoperative complications occur in 59% of all esophagectomy patients (Table 17.2) [14]. Great emphasis has been placed on identifying patients at increased risk for specific postoperative complications after esophagectomy, which provides the means to mitigate risk and to provide additional monitoring or interventions postoperatively.

Pulmonary

The most common complications after esophagectomy are pulmonary, with pneumonia occurring in 14.6% of patients. Two-thirds of deaths after esophagectomy occur in patients with documented pulmonary complications [15–17]. Such complications are also associated with a tenfold higher postoperative mortality rate and significantly shortened life expectancy [18, 19]. Predictors of postoperative pulmonary complications include low forced expiratory volume in the first second (FEV1), administration of preoperative radiation, extremes of BMI, poor performance status, and advanced age [18–21]. Given the prevalence and impact of pulmonary complications, a risk scoring system has been developed to assess relative risk of postoperative pulmonary complications based on weighted scores for FEV_1, diffusing capacity of the lung for carbon monoxide (DLCO), age, and performance status (Fig. 17.1) [22].

Postoperative pulmonary complications are more common in patients with reduced FEV_1, lower DLCO after induction therapy, and in those receiving higher doses of radiation [18]. In addition, patients with low or very high body mass index (BMI) have an increased incidence of pulmonary complications compared to patients with normal BMI [21, 23, 24].

Because of the morbidity and mortality associated with pulmonary complications, it is vital to employ measures to reduce their incidence. These measures include preoperative respiratory rehabilitation (smoking cessation, inspiratory muscle training) [25, 26], enhanced oral hygiene including frequent preoperative teeth brushing [27], postoperative pulmonary toilet maneuvers, and adequate postoperative pain management [26].

Assigned score value	0	1	2	3	4
Age	<50	51-60	61-70	71-80	>80
Performance Status (Zubrod/ECOG)	0	1	2	3	4
FEV1%	≥100	90-99.9	80-89.9	70-79.9	<70
DLCO%	≥100	90-99.9	80-89.9	70-79.9	<70

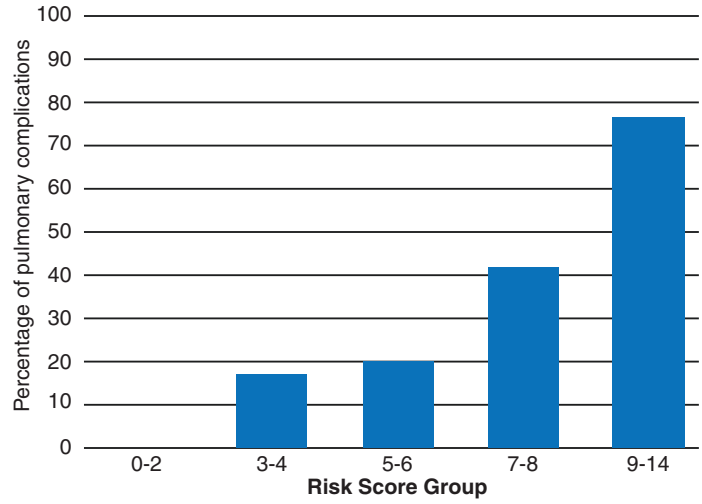


Fig. 17.1 Incidence postoperative pulmonary complications categorized by assigned risk score based on age, perfomance status zubrod/eastern cooperative oncology group (ECOG), forced expiratory volume in the first second (FEV1), and diffusing capacity of the lung for carbon monoxide (DLCO). From Reinersman et al. with permission [22]

Cardiovascular

Atrial Dysrhythmias

Atrial dysrhythmias such as atrial fibrillation (AF) occur in 14.5% of esophagectomy patients [28, 29]. When AF occurs, there should be a high index of suspicion for other complications such as anastomotic leak and pneumonia. As an isolated event, AF is associated with an increase in hospital length of stay, a possible need for medical intervention, and important patient distress. Prevention of postoperative AF begins with preoperative optimization of modifiable risk factors such as cardiac disease, smoking, and alcohol abuse [30]. All patients taking a preoperative beta-blocker should continue it perioperatively. Esophagectomy is classified as a high risk procedure, and guidelines indicate that anyone who has preserved left ventricular function and is not taking a beta-blocker should be managed with perioperative prophylactic diltiazem or amiodarone [30].

Major Adverse Cardiac Events

A brief cardiac and medical history and assessment of activity level is sufficient to determine which patients need a preoperative cardiac workup. Level of activity is classified in terms of metabolic equivalents (METs). The risk of a major adverse cardiac event (MACE) can be calculated using the Revised Cardiac Risk Index for Pre-Operative Risk (Fig. 17.2) [31], which incorporates the type of surgery and a history of congestive heart failure, ischemic heart disease, cerebrovascular disease, or creatinine >2 mg/dl. Patients who are low risk (<1% risk of MACE) require no additional workup. Among patients at increased risk of MACE, no additional testing is indicated if they can climb a flight of stairs or walk on level ground at 3–4 mph (equivalent to ≥4 METs). For patients who are at increased risk and have an exercise ability <4 METs or that cannot be determined, further workup is suggested [31].

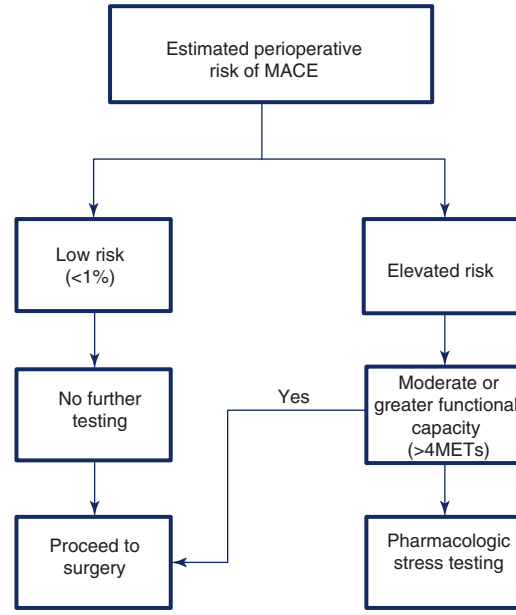


Fig. 17.2 Use of the Revised Cardiac Risk Index for determining which patients require preoperative cardiac evaluation. *MACE* major adverse cardiac events, *METs* metabolic equivalents. Modified from Fleisher et al. with permission [31]

Venous Thromboembolism

The risks of pulmonary embolism, deep venous thrombosis and venous thromboembolism (VTE) after esohphagectomy are about 2%, 4% and 5%, respectively, and over 80% of post-esophagectomy VTE events occur during the postoperative hospitalization. Risk factors for in hospital VTE are male sex, white race, prolonged ventilation, and other major complications of surgery. Risk factors for post-discharge VTE are advanced age and major postoperative complications. VTE prophylaxis includes pharmacologic and mechanical measures, should be routine, and should be started prior to induction of anesthesia. Currently there is no consensus on the duration of postoperative prophylaxis. However, elderly patients and patients with major postoperative complications are most likely to benefit from extended-duration (4–6 weeks) chemoprophylaxis [32].

Intraoperative Management

Fluid Administration

Perioperative fluid management to maintain euvolemia improves recovery of postoperative gastric emptying and bowel function and reduces morbidity [33–35]. This is achieved by strict

intraoperative and postoperative monitoring of fluid intake and output, avoidance of unnecessary intravenous fluid administration including transfusions, and 'permissive oliguria' in appropriately selected patients [36].

Maintenance of Body Temperature

Maintenance of normothermia is associated with a reduction in wound infections, cardiac complications, bleeding, and transfusion requirements [37–40]. For this reason, accurate, noninvasive, and continuous intraoperative temperature monitoring is essential. Forced air heating covers should be used for all patients undergoing esophagectomy. In the event of intraoperative hypothermia, warmed intravenous fluids should be used. For rapid rewarming, infusion of warm saline intraperitoneally or intrapleurally is an additional effective strategy.

Anesthetic Considerations

Perioperative pain management should be preemptive and multimodal. Initiation of neuroaxial blockade before surgery and its maintenance throughout surgery decreases the need for anesthetic agents, opioids and muscle relaxants [41]. Non-steroidal anti-inflammatory agents in conjunction with acetaminophen and gabapentinoids reduce the need for postoperative analgesia [41]. The use of low dose propofol (<20 mcg/kg/min) with avoidance of inhalation anesthetics reduces PONV and should be considered for all patients [13].

Carbohydrate Loading

Preoperative carbohydrate loading with a high-calorie (12.5% carbohydrate, 400 ml) clear drink 2 h before surgery decreases insulin resistance, improves gastric emptying, improves patient well-being, and may reduce duration of hospital stay [42]. Importantly, it has not been shown to increase the risk of perioperative aspiration.

Postoperative Management

Pain Management

The goals of pain control after esophagectomy are to permit deep breathing, prevent atelectasis, and allow unhindered ambulation, while reducing the use of opioids. The goal is to achieve a pain score of 4 out of 10. This can be accomplished with the use of intraoperative local and regional anesthesia placed prior to incisions and at the end of the operation, and a multimodal perioperative regimen including acetaminophen, non-steroidal anti-inflammatories and gabapentinoids, with a limited amount of narcotic available for breakthrough pain. Patient controlled analgesia (PCA) can be added if pain scores remain >4 following initial use of the narcotics. In patients undergoing a thoracotomy, neural blockade can be employed, and there is no clear evidence demonstrating superiority of a paravertebral block or an epidural block. Some studies suggest a reduction in minor procedure-related complications with the use of paravertebral blocks and reduced use of additional analgesic modalities with the use of epidurals [43]. Patients should be assessed early and regularly in order to make appropriate adjustments to pain medications and reinforce the importance of deep breathing and ambulation.

Early Mobilization

Early ambulation in surgical patients reduces pain scores and postoperative pulmonary complications and improves patient satisfaction [44]. Early ambulation within hours of surgery is feasible and safe [45]. Patients can be placed in a chair upon arrival in their room and should be encouraged to ambulate with assistance as soon as possible on the day of surgery.

Diet and Nutrition

Weight loss is common both pre- and postoperatively in patients with esophageal cancer [46]. Traditionally, patients have been restricted to 'nothing by mouth' after midnight on the night prior to surgery. Prolonged fasting aggravates the surgical stress response, increases insulin resis-

tance, exaggerates protein losses, and impairs gastrointestinal function [47–50]. It also increases the time to resolution of negative protein balance and anabolism. From a patient-centered standpoint, fasting results in unnecessary symptoms such as thirst, hunger, headaches and anxiety. In contrast, early postoperative alimentation decreases time to neutral protein balance, reduces wound and pulmonary infections, decreases the incidence of anastomotic leak, and is associated with shorter length of hospital stay [51]. Postoperatively, the nasogastric tube can be removed on the first postoperative day if the output is minimal and there is no radiographic evidence of conduit dilation, and a clear liquid diet can be started shortly thereafter.

Routine Postoperative Anastomotic Evaluation

It is common practice in many centers to perform a postoperative swallow evaluation or endoscopy prior to initiating a diet. However, routine postoperative anastomotic evaluation is ineffective in diagnosing subclinical leaks and thus does not change outcomes. The positive predictive value of routine postoperative endoscopy and contrast swallow are 8% and 3%, respectively [52]. In the absence of a clear indication for evaluation, anastomotic evaluation is unnecessary, costly, bears an inherent risk of aspiration, and may delay oral alimentation and discharge.

Complications and Their Management

Postoperative complications after esophagectomy can result in important patient distress, prolonged hospital stay, delayed or incomplete recovery, delay in initiation of adjuvant treatment, and death [53]. Vigilance, early identification, and appropriate intervention in the event of postoperative complications are important to minimize the impact on the patient's recovery.

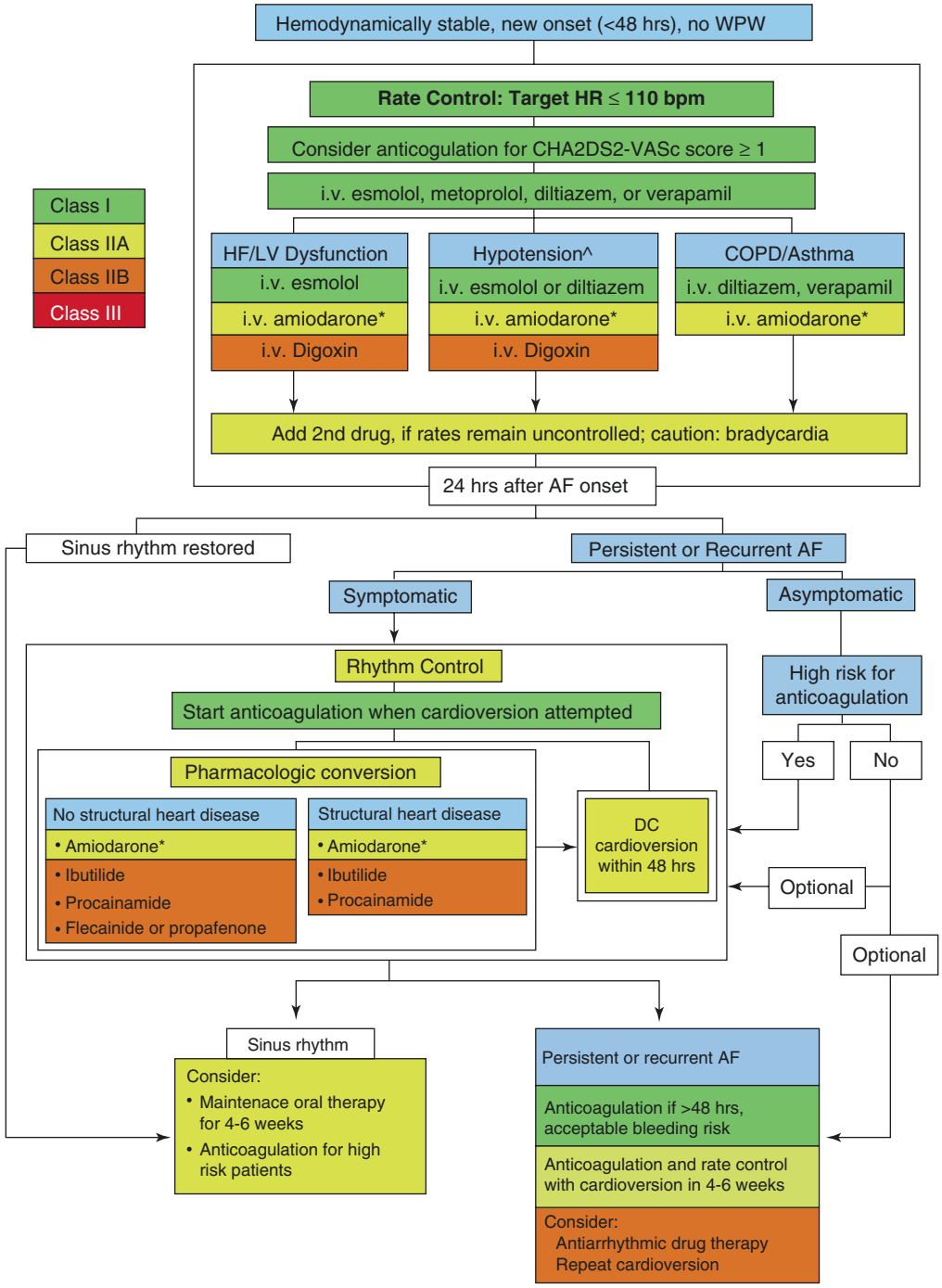
Pulmonary

Despite preventive measures, postoperative atelectasis, aspiration and pneumonia remain the most common postoperative complications in esophagectomy patients. Atelectasis may be asymptomatic or present as an increased work of breathing or hypoxemia. Treatment is guided by the presence or absence of secretions. If the patient has no secretions, first line therapy includes deep breathing exercises and incentive spirometry. If this is unsuccessful, continuous positive airway pressure reduces the incidence of reintubation and pneumonia [54]. In patients with excessive secretions, first line treatment is mucus clearance through frequent suctioning and chest physiotherapy. The use of bronchoscopy has been frequently reported but no clear benefit has been demonstrated [55].

The diagnosis of postoperative pneumonia can be challenging. The use of standard diagnostic criteria for hospital acquired pneumonia results in over diagnosis [56]. Postoperative pneumonia should be suspected in a patient with clinical signs of infection (fever, purulent sputum, leukocytosis or leukopenia and worsening oxygenation) and a new radiographic infiltrate. Treatment of hospital acquired pneumonia in high risk patients is guided by institutional microbiological sensitivity data and infectious disease guidelines.

Atrial Fibrillation

The goals of management of AF are: (1) reduce or stop catecholaminergic inotropic agents; (2) optimize fluid balance; and (3) evaluate for the presence of and treat all possible correctable triggering factors. These include bleeding, pulmonary embolism, pneumothorax, pericardial irritation, myocardial infarction, and mediastinal infection. In the hemodynamically unstable patient, synchronized cardioversion is indicated. In the hemodynamically stable patient, the immediate goal is rate control (heart rate <110 bpm). Intravenous esmolol, metoprolol, diltiazem, or verapamil are each recommended for use. In the presence of heart failure, esmolol is preferred. If the patient is hypotensive, esmolol or diltazem are the drugs of choice, whereas in the presence of chronic obstructive pulmonary disease (COPD) or asthma, diltiazem or verapamil are preferred (Fig. 17.3) [30].



*Caution should be exercised and a TEE considered if amiodarone is used after 48 hours after the onset AF, as there is a possibility that the rhythm could convert with risk of thromboembolism.
^Esmolol or diltiazem first line depending on degree of hypotension

Fig. 17.3 Management of postoperative atrial fibrillation less than 48 h in duration in a hemodynamically stable patient. Reproduced with permission from Frendl et al. [30]. *WPW* Wolff Parkinson White, *HR* hear rate, *i.v.* intravenous, *HR* heart rate, *LV* left ventricular, *COPD* chronic obstructive pulmonary disease, *AF* atrial fibrillation, *DC* direct current, *TEE* trans esophageal echocardiography

Chylothorax

Injury to the thoracic duct is associated with mortality rates as high as 18% [57, 58]. The diagnosis should be considered when there is a high chest tube output or a change in the nature of the output to a milky appearance with enteral alimentation. It is confirmed with a pleural fluid triglyceride level >110 mg/dl or a fluid triglyceride level of 50 mm/dl and the finding of chylomicrons in the pleural fluid [59, 60]. Once a diagnosis is established, the tenets of management are: (1) drainage of the pleural space; (2) reduction of lymph flow; and (3) maintenance of hydration and nutrition.

Medium chain triglyceride (MCT) diets have been used with variable success. This widely practiced approach is predicated on the fact that MCTs are taken up preferentially by the portal system and thus bypass the thoracic duct system. This effect, however, appears to be mitigated by the fact that oral intake stimulates chyle production. For this reason, many authors advocate complete bowel rest and parenteral nutrition. Octreotide, a somatostatin analog, acts on somatostatin receptors to reduce the flow of thoracic duct lymph by reducing gastric, biliary and pancreatic secretions, and to inhibit absorption from the intestine. It is an effective adjunct to operative or non-operative management [61].

A short course of nonoperative management of a chylothorax with a pleural drainage tube in place is appropriate. However, if the leak persists at >10 ml/kg for a few days, it is unlikely to resolve without further intervention [62]. When non-operative management has failed, postsurgical chylothorax is usually managed with thoracic duct ligation. This can be performed by a thoracoscopic or open approach. This decision is based on the clinical scenario and local expertise [63, 64]. In order to identify the leak intraoperatively, dairy cream or olive oil mixed with lipophilic dye may be administered via a nasogastric or jejunal feeding tube 20 min prior to anesthetic induction.

Access to the thoracic duct injury is usually via the side with the chylothorax. However, the approach to esophageal resection, the type of reconstruction, and the unique anatomy of the patient's duct may affect the approach. When the leak is identified, direct ligation of the duct is performed with non-absorbable ligatures above and below the level of injury. If the duct injury cannot be identified then mass ligation is used, which includes all tissues located between the aorta and the azygous vein. This is most easily performed via the right chest just above the diaphragmatic hiatus. In these cases care is taken not to injure the conduit or its blood supply.

Thoracic duct embolization is described as an alternative nonsurgical method of chylothorax treatment. There are several methods for accessing the cisterna chyli [65–67], the most common of which is direct trans-abdominal percutaneous needle cannulation. Contrast is used to identify the source of the leak and the affected segment is embolized with coils or glue. This approach has been employed most often in patients who are poor operative candidates or have failed operative management. Experience with thoracic duct embolization is limited and no randomized trials exist. Given the low morbidity rates and promising case series, this approach may be attempted prior to surgical intervention in centers with appropriate experience.

Anastomotic Leak

Despite the advent of new methods of treatment (intraluminal stents, suction devices), the basic tenets of esophageal anastomotic leak management continue to include [68]:

1. Adequate drainage via surgical exposure, pleural catheter insertion and/or intraluminal drainage such as nasogastric tube or vacuum sponge
2. Initiation of broad-spectrum antibiotics often including antifungal agents
3. Optimizing nutritional status via enteral or parenteral feeding.

For clinically important leaks, early endoscopy is often indicated to differentiate between anastomotic leaks limited to defects in the anas-

tomosis with healthy surrounding tissues versus conduit necrosis, as the clinical management of these two entities differs significantly.

Contained anastomotic leaks are defined as leaks in which contrast material extravasates outside the alimentary lumen to a limited extent and gathers in a well-defined and small collection. Patients with contained leaks are by definition minimally symptomatic. Uncontained leaks are characterized by free extravasation of intraluminal contents into the space surrounding the anastomosis, often with extension into the pleural space or mediastinum. Cervical anastomotic leaks have a low morbidity and mortality rate compared to intrathoracic leaks. This is due primarily to the relatively lower rate of mediastinitis and empyema. In contrast, the severity of thoracic anastomotic leaks is highly variable, from asymptomatic to severe sepsis with multi-organ dysfunction. Table 17.3 demonstrates a method of classification of esophageal leaks by the Esophagectomy Complications Consensus Group (ECCG) [28].

Cervical Anastomotic Leaks

Small contained cervical leaks are managed with observation and maintenance of a clear liquid diet. Larger contained cervical leaks can often be managed successfully by opening and packing of the wound and less commonly with closed drain placement, if one is not already in place. Leaks that are large, uncontained, or are accompanied by signs of sepsis more often require examination under general anesthesia, copious irrigation and, if possible, attempted repair and muscle flap coverage [69].

Table 17.3 Classification of esophageal leaks [28]

Classification	Description
Type I	Local defect requiring no change in therapy or treated medically or with dietary modification
Type II	Localized defect requiring interventional but not surgical therapy; for example, interventional radiology drain, stent or bedside opening, and packing of incision
Type III	Localized defect requiring surgical therapy

Thoracic Anastomotic Leaks

In the stable patient, initial work-up should include imaging and endoscopic evaluation. Chest computed tomography should be performed early in the course of the treatment to determine if there are undrained fluid collections. Endoscopy provides an assessment of the severity of disruption and necrosis as well as enabling interventions such as covered stent placement. Conduit necrosis, if present, is classified using the ECCG grading system (Table 17.4) [28]. Stents have shown promise in permitting early oral feeding and reduction of leakage of intraluminal contents [70]. Conversely, there is concern that the radial force of the expandable stent could cause worsening local ischemia [71, 72]. Stent migration occurs in 75% of patients [73], although the problem is less frequent with increased experience and with the use of endoscopic fixation techniques. Stent erosion and ingrowth limit the time that they can be left in place [70, 74].

The decision must be made whether the patient should be managed operatively or non-operatively. This is based on the patient's clinical status, the level of extraluminal contamination, and the presence or absence of conduit necrosis. Small contained leaks can often be managed without intervention. Conversely, the presence hemodynamic instability, extensive intrathoracic/mediastinal contamination, or Type II or III conduit necrosis requires intervention. This may include thoracostomy tube placement, stenting,

Table 17.4 Classification of esophageal conduit necrosis [28]

Classification	Description
Type I	Conduit necrosis focal
	Identified endoscopically
	Treatment is additional monitoring or non-surgical therapy
Type II	Conduit necrosis focal
	Identified endoscopically and not associated with free anastomotic or conduit leak
	Treatment is surgical therapy not involving esophageal diversion
Type III	Conduit necrosis extensive
	Treated with conduit resection with diversion

and/or an operation. When an operation is deemed necessary and the leak is in not accompanied by extensive conduit necrosis, all devitalized tissue should be debrided from the site. Primary repair of the leak should be considered, even if the diagnosis is delayed. Coverage with a vascularized pedicled flap may aid in healing. The most commonly used flaps include intercostal muscle, latissimus dorsi, serratus anterior, pericardium, pleura, and omentum. The area surrounding the repair should be widely drained. In the rare case of a type III conduit necrosis, conduit resection and proximal salivary diversion must be performed.

Delayed Gastric Emptying

Delayed gastric emptying is common after esophagectomy, occurring in approximately 20% of patients. This is due to a relative ischemia of the neoesophagus, loss of parasympathetic innervation of the pylorus, and transposition of the stomach into the negatively pressured chest. It is important to rule out gastric outlet obstruction by swallow evaluation or endoscopy. When present, this can be treated with pyloric balloon dilation and/or botulinum toxin injection with good results [75].

Erythromycin is a motilin receptor agonist which induces migrating motor complexes by stimulating the motilin receptors in the gastric antrum and duodenum, resulting in improved gastric emptying. The major limitation of erythromycin is tachyphylaxis (diminishing effectiveness over time) due to the down-regulation of motilin receptors. The medication can be held for 2 weeks and then resumed. Metoclopromide is a dopaminergic agonist which is a good second line therapy, although there is a 1% risk of tardive dyskinesia. Patients must be instructed to stop the medication if they develop involuntary body movements. Domperidone is another second line medication that can be prescribed with new investigational drug clearance from the Food and Drug Administration. It has been shown to be as effective as metoclopromide, with less central nervous system side effects. It can prolong the QT interval, and a baseline EKG should be performed [76].

Intermediate-term measures are most appropriate in the immediate postoperative period. Resolution of delayed gastric emptying usually occurs over time, and has been attributed to increased involvement of the myenteric plexus in pyloric function and gastric motility [77]. In instances in which delayed gastric emptying is unremitting despite pharmacologic and endoscopic intervention, pyloromyotomy or pyloroplasty can be considered.

Conclusions

Appropriate preoperative risk-stratification using known risk factors for adverse outcomes can assist in properly identifying suitable candidates for resection and recognizing potentially modifiable risk factors. Perioperative care plans in the context of enhanced recovery after surgery (ERAS) reduce adverse outcomes. ERAS interventions are designed to minimize the impact of surgery on the patient, thus reducing postoperative complications, minimizing length of hospital stay, and lowering costs. Preoperatively, these include multimodal patient education, PONV screening, and minimizing the effects of preoperative fasting. Intra-operative elements include preemptive multimodal analgesia, prophylactic antiemetics, minimizing fluid administration, and permissive oliguria. Postoperatively these include early ambulation, multimodal pain control, and early alimentation. When postoperative complications occur, prompt identification and appropriate management can reduce their negative sequelae.

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18 Volume and Outcomes in Esophageal Cancer Surgery

Francisco Schlottmann, Fernando A. M. Herbella, and Marco G. Patti

Relationship Between Volume and Outcomes in Esophageal Cancer Surgery

The incidence of esophageal cancer, particularly esophageal adenocarcinoma, is expected to rise dramatically in many Western countries [1]. Surgical resection is the cornerstone of curative treatment. Although there has been a significant improvement in operative techniques and postoperative care, esophagectomy remains one of the most demanding surgical procedures with significant associated morbidity and mortality [2, 3].

Birkmeyer et al. [4] examined the relationship between hospital volume and surgical mortality in six different types of cardiovascular procedures and eight types of major cancer resections. Esophagectomy showed one of the most dramatic differences in mortality between very low volume (<2 procedures/year) and very high volume hospitals (>19 procedures/year) (18.9% vs. 8.1%). Wouters et al. [5] analyzed a cohort of patients who underwent esophagectomy after a centralization project in The Netherlands. Eleven hospitals in the mid-western part of the country were affiliated to the Comprehensive Care Center West. They found that along with a reduction in postoperative morbidity and length of stay, mortality fell from 12% to 4% and survival improved significantly after centralizing esophageal resections. Markar et al. [6] performed a meta-analysis comprising 27,843 esophagectomy operations. Esophagectomy at low volume hospitals was associated with a significant increase in incidence of in-hospital mortality (8.48% vs. 2.82%) and 30-day mortality (2.09% vs. 0.73%). A recent European multicenter study included 2,944 consecutive patients undergoing esophagectomy for esophageal cancer in 30 centers between 2000 and 2010 [7]. The study found that low volume hospitals were significantly associated with increased 30-day mortality, and postoperative mortality secondary to anastomotic leak and pulmonary- and cardiac-related causes [7].

We recently performed a retrospective population-based analysis using the National Inpatient Sample for the period 2000–2014, including patients diagnosed with esophageal cancer and

F. Schlottmann (✉)
Department of Surgery, Hospital Alemán of Buenos Aires, University of Buenos Aires, Buenos Aires, Argentina

F. A. M. Herbella
Department of Surgery, Federal University of Sao Paulo, Sao Paulo, Brazil
e-mail: herbella.dcir@epm.br

M. G. Patti
Department of Medicine and Surgery, University of North Carolina, Chapel Hill, NC, USA
e-mail: marco_patti@med.unc.edu

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who underwent esophagectomy during their inpatient hospitalization [8]. Yearly hospital volume was categorized as low (<5 procedures), intermediate (5–20 procedures), and high (>20 procedures). Esophagectomy at low and intermediate volume hospitals, as compared to high volume hospitals, was associated with a significant increase in mortality (low volume OR 2.17, 95% CI 1.49–3.15, $p < 0.0001$ and intermediate volume OR 1.62, 95% CI 1.20–2.17, $p = 0.002$). Interestingly, the percentage of esophagectomies performed at high volume centers significantly increased during the study period (29.2% in 2000 and 68.5% in 2014, $p < 0.0001$). This voluntary centralization was associated with a dramatic decrease in the mortality rate, which dropped from 10.0% to 3.5%, $p = 0.006$ (Fig. 18.1).

The better outcomes achieved in high volume centers could be explained by many reasons:

- Multidisciplinary approach for esophageal cancer management with better patient selection
- Advanced surgical techniques
- Dedicated anesthetic teams
- High dependency units
- Enhanced perioperative care

Centralization of Cancer Care

Centralizing cancer care into specialized centers may offer two significant advantages: this may assure that all cancer patients will seek treatment in designated centers for excellence, and benefit access to high quality care for vulnerable populations. The Netherlands is a remarkable example of centralization of cancer treatment. The Dutch Cancer Society formed a "Quality of Cancer Care Taskforce" in 2007, comprising medical specialists from all disciplines involved in the care for cancer patients who had expertise in quality of care improvement projects. The taskforce focused on the relation between procedural volume and patient outcome, and concluded that variation in quality of care for cancer patients in The Netherlands varied by hospital structural characteristics such as diagnostic and procedural volume, and academic or teaching status. As a result, The Netherlands Health Care Inspectorate intervened and prohibited the performance of certain cancer procedures in certain hospitals (e.g. banned esophagectomies from hospitals with a mean annual volume less than 10) [9].

Community-based cancer care facilities might be a logical strategy in disadvantaged communities. In a

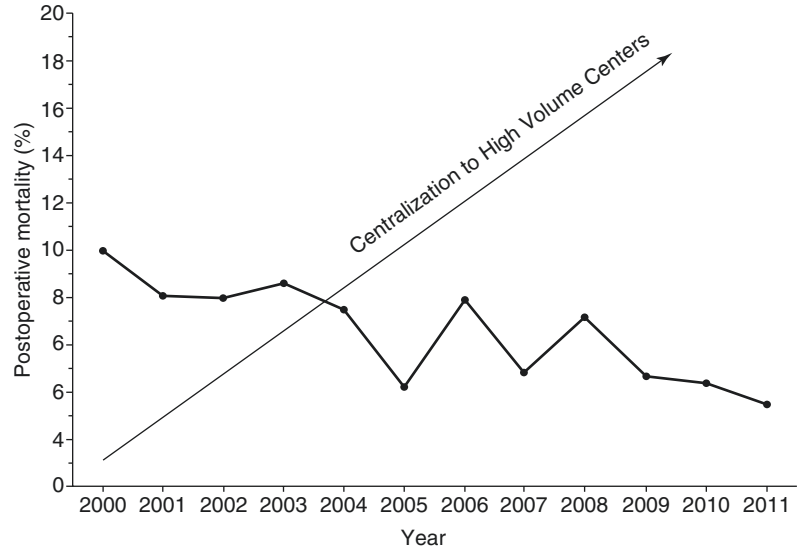

Fig. 18.1 Centralization of esophagectomy procedures towards high volume hospitals decreased postoperative mortality rates in the US between 2000 and 2011 (Data extracted from Schlottmann et al. [8])

centralized network, patients would then need to travel to seek treatment in regional center of excellence. In fact, a recent study reported that esophageal cancer patients who travel longer distances to high volume centers receive different treatment modalities and obtain better outcomes than do patients who stay close to home at low volume centers [10]. However, with the lack of uniform prescriptive guidelines or volume standards implementation, the attainment of centralization of cancer care is challenging. We can attribute this to several variables:

(1) Many patients prefer to seek definitive cancer care near home at local community hospital, rather than in an unknown center far from their support network.
(2) Determining how patients would be transported to specialized regional centers is complex (especially in large countries).
(3) Designating centers of excellence and steering patient referrals to such centers is intricate. Where to set the bar to define excellence will be also complex.
(4) The financial implications of patient referral to high volume centers may be a disincentive to centralization of care. Health care systems encourage referral to in-system providers in order to maintain market share. In addition, physicians may establish referral patterns based on likelihood of retaining patients after treatment.

These obstacles above imply that profound policy changes are needed to develop a centralized cancer network. Such ambitious reform may not be feasible from one day to the other. The development of regional cancer care networks is a reasonable strategy. In the United States, for example, the University of Pittsburg Medical Center (UPMC) is a promising example. They established the UPMC Cancer Center that is one of the largest oncology networks in the US. This network include a large number of medical facilities and treats more than 74,000 patients each year in Pennsylvania, West Virginia, and Ohio. The UPMC Cancer Center includes a regional hub and satellite facilities, allowing for coordination of patient care across facilities and physician groups. Through this system, patients benefit from improved access at satellite locations and safely referrals for further treatment at central facilities [11].

Health care providers and payers will need to address the economic burden of a centralized cancer care system. Even if specialized treatment facilities are located in areas where travel time is longer for esophageal cancer patients, treatment may still be most efficient if provided at these core facilities.

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19 Quality of Life After Esophagectomy

Melissa DeSouza, Claire L. Donohoe, and James P. Dolan

Introduction

Historically, the exceedingly high mortality and morbidity associated with esophagectomy prohibited any meaningful consideration of postoperative quality of life. It is only recently that treatment paradigms have evolved to the extent that health-related quality of life (HRQL) can be recorded and analyzed. This is related to two important observations. First, current improvement in patient selection and peri-operative care has meant that esophagectomy can now be performed safely with a 2–3% 30-day post-operative mortality rate in experienced centers, even in the face of a morbidity rate of up to 20% [1]. Second, as prognosis for patients treated with curative intent improves, long-term quality of life outcomes become increasingly important. In the 1970s, long-term survival following diagnosis of esophageal cancer with curative intent was less than 5% [2]. In the twenty-first century, 5-year survival data from the CROSS (Chemoradiotherapy for Oesophageal cancer followed by Surgery Study) trial reported overall 5-year survival rates of 47% [3] with institutional series reporting survival as high as 60% [1]. As a result, cure alone is no longer the sole outcome of interest for patients with esophageal cancer. This chapter will focus on patients undergoing esophagectomy for esophageal or esophagogastric cancer with the aim of detailing short- and long-term patient-related quality of life (QL) outcomes.

What Is Health-Related Quality of Life, and Why Measure It?

Health-related quality of life (HRQL) is a multidimensional concept that includes physical, emotional, mental, and social functioning. These domains, and a number of other components, form a collective framework that helps to define the overall HRQL after the impact of major disease or surgical disability [4]. Well-being is one of these, and is related to HRQL by assessing positive aspects of life, such as life satisfaction and emotions, against a backdrop of a specific disease or condition that afflicts an individual [5]. A patient-reported outcome (PRO) is a different component of assessment. This is any report of the status of an individual patient's health condition that is reported directly by the patient [6]. Examples of PROs include symptoms (which

M. DeSouza · C. L. Donohoe · J. P. Dolan (✉)
Division of Gastrointestinal and General Surgery, Oregon Health and Science University, Portland, OR, USA
e-mail: desouza@ohsu.edu; donohoe@ohsu.edu; dolanj@ohsu.edu

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may be physical or psychological), function (which may be physical, emotional, or social), and the impact of disease or treatment on daily life. Patient-centered outcome (PCO) is another health-related quality index that details outcomes from medical care that are important to patients themselves [7]. PCOs have received fresh interest in the management of chronic diseases, where they have been used to improve quality of life by tracking symptom or functional changes and to enhance patient-physician communication [8].

To date, most reports that have examined esophageal cancer outcomes have focused on peri-operative outcomes, and most consistently demonstrate a reduction in HRQL in the first 6 months following surgery [9]. Unfortunately, there is a paucity of high quality long-term PROs for those who have undergone treatment for esophageal cancer. Consequently, it is not surprising that we lack a clear understanding of each patient's expected function, well-being and health needs over the long-term.

HRQL is the most commonly used index for a patient-assessed, disease-specific, or generic, questionnaire that measures quality of life across a number of domains including, physical, social, and emotional functions. Once collected and analyzed, these data should be expected to provide clinicians with meaningful information to guide the application of treatments. In parallel, these data should also provide a framework for patient-centered prospective interventions that may enhance well-being, PRO, and overall HRQL after treatment.

The most commonly used instruments [9] (Table 19.1) are held to be reliable and valid, but their application to the post-surgical clinical setting has been limited. One major concern is how to usefully express the information that they convey to patients as they recover from surgery, in order to track the individual recovery or identify points for intervention to optimize HRQL. Gastrointestinal issues, for example, are commonly experienced after esophagectomy, but their extent and duration are not well understood. Hence, the ability to distinguish between what may be expected to occur in the majority of patients from what may be pathologic with regard to experiencing dumping symptoms is challenging.

Validated HRQL measures have been widely reported in oncology clinical trials. These reports, however, have largely failed to communicate the effect of treatment on HRQL to patients, or even how to compare HRQL outcomes against other outcomes such as cure, mortality, or morbidity. Indeed, while HRQL is viewed by physicians as an important outcome for clinical trials, it is viewed as the least important domain, when compared with those such as complications from treatment, prognostic outcomes (survival/recurrence), and hospital length of stay. When physicians value HRQL as important outcome in clinical trials, these data become useful in clinical decision making with patients [10].

Doctors and other health care professionals who specialize in the treatment of certain conditions do not necessarily perceive disease or treatment-related outcomes in the same way as patients who actually have the condition. This is illustrated by the fact that patients rate quality of life as an extremely important outcome after treatment for esophageal cancer. Using the Toronto Information Needs Questionnaire, a validated tool for assessment of information preferences, 82% of 136 patients with esophagogastric cancer considered information about long-term quality of life outcomes as very or extremely important [11].

In other studies, patients report that although cure is important, quality of life is more important. In a study of 81 post-operative patients with esophagogastric cancer and 90 specialist doctors, participants were asked to complete a discrete-choice questionnaire of hypothetical scenarios differing according to their mortality, morbidity, quality-of-life, cure rate, hospital type, and the reputation of the surgeon [12]. Interestingly, patients were willing to risk a higher post-operative mortality and higher cure rate for a better long-term quality of life. On the other hand, doctors were less likely to risk higher post-operative mortality than patients.

Clinicians generally rate short-term clinical outcomes, such as complications, highest among core outcomes sets provided to patients prior to surgery, while patients prioritize information related to long-term benefits above short-term

Table 19.1 Currently employed tools for assessing HRQL in esophageal cancer

Questionnaire	Target population	Dimensions (number of items)
SF-36 [44]	General population	Vitality (4)
		Physical (10)
		Pain (2)
		General health perceptions (5)
		Physical role functioning (4)
		Emotional role functioning (3)
		Social role functioning (2)
		Mental health (5)
		Health changes (1)
EORTC QLQ-C30 [45]	Cancer patients	Global health (2)
		Physical function (5)
		Social function (2)
		Emotional function (4)
		Cognitive function (2)
		Role function (2)
		Fatigue (3)
		Pain (2)
		Nausea and vomiting (2)
		Single items (6)
EORTC QLQ-OES18 [46]	Esophageal cancer patients	18 single items specific to esophageal cancer
FACT-E [47]	Esophageal cancer patients	17 single items specific to esophageal cancer
DAUGS20 [48]	Post-op esophageal cancer patients	20 single items specific to esophageal cancer
Esophageal and Stomach Symptom Scale (ES4) [49]	Post-op esophageal cancer patients	Cervico-thoracic symptoms (reflux, heartburn or stricture), Abdominal hypersensitivity symptoms, Abdominal distension symptoms
		Diet induced systemic symptoms
Esophago-gastric surgery and Quality of Dietary Life (EGQ-D) scale [50]	Post-op esophageal cancer patients	8 single items specific to esophageal cancer

complications [13]. In studies where the two different information needs were balanced (i.e. the needs of patients and those of physicians), the consensus was that specific aspects of esophagectomy should be considered and discussed during pre-operative counselling and reported in clinical trial outcomes. These included: in-hospital milestones to recovery, rates of open and laparoscopic surgery, in-hospital mortality, major complications, and milestones in recovery after discharge, including long-term eating and drinking, overall quality of life, and chances of survival.

Taken together, these studies indicate that there is a need to understand the trajectory of quality of life changes in the treatment and recovery process during patient to physician communication, as well as to define commonly encountered issues in symptoms and function that may be improved in order to enhance long-term HRQL.

Peri-Operative Quality of Life Through the First 6 Months After Surgery

Several patient factors are related to poor postoperative quality of life. The presence of comorbidities is associated with poor global and physical role function; younger patients have poorer emotional coping scores than patients over 60 years of age, and worse baseline symptoms are predictive of poor postoperative HRQL [14]. Specific tumor

factors have also been shown to predict poor quality of life, such as location in the upper third of the esophagus, and stage III or IV tumors [14].

Preoperative Assessment of Health-Related Quality of Life and Prognosis

HRQL has been found to be a predictor of postoperative outcomes and survival in several types of cancer, including esophagogastric cancer [15]. Self-reported measures of HRQL may reflect intrinsic patient perception of their own disease course, suggesting disease recurrence before it becomes clinically or radiographically apparent [16, 17].

In a study comparing baseline (pre-treatment) HRQL to scores at 6 months post-treatment, better recovery of physical function score was associated with a lower 5-year mortality, while increased patient reports of fatigue and pain were associated with higher risk of death [16]. Pain has been recognized as a clinical sign of recurrence, and is often reported to be associated with advanced disease. In a Swedish nationwide study of patients with newly diagnosed esophageal cancer, Djarv and Lagergren identified a 29–69% increase in mortality in patients with poor HRQL scores. There was a 55% increase in the risk of death among patients who reported a poor global quality of life prior to treatment, when compared to those who reported good global quality of life (HR = 1.55; 95% CI 1.19–2.02) [15]. A similar increase in mortality was seen in patients who reported poorer social function, physical function, pain, and dyspnea. These authors also found that the highest hazard ratios for death were seen in patients who reported symptomatic fatigue 6 months post-operatively (HR = 1.65; 95% CI 1.30–2.11), and in patients with symptomatic appetite loss (HR = 1.69; 95% CI 1.32–2.14) and dysphagia (HR = 1.69; 95%CI 1.13–2.51) [15]. McKernan et al. assessed a significantly smaller cohort (152 patients), and only appetite loss remained an independent predictor of cancer-specific survival after adjustment for tumor stage and treatment [17].

In addition to patient-reported quality of life measures, clinical and physiological measures have also been utilized to predict postoperative outcomes. Healy et al. found that dyspnea at time of diagnosis was an independent predictor of in-hospital mortality on multivariate analysis. Further, worsened fatigue at diagnosis was found to be predictive of decreased 1-year survival, when adjusting for known confounding variables [18].

Effect of Neoadjuvant Therapy on Health-Related Quality of Life

After the CROSS study demonstrated a survival benefit in favor of trimodality therapy, there has been a marked increase in the use of neoadjuvant therapy for locally advanced esophageal carcinoma [3]. A subset of the CROSS trial was subjected to HRQL testing as a secondary endpoint. A decline in all endpoints (including global quality of living, physical function, fatigue, eating problems, and emotional problems) was seen in the neoadjuvant chemoradiation group 1 week after completion of therapy [19]. There was no apparent effect of neoadjuvant chemoradiation on HRQL on patients in the post-operative period, when compared with those who received surgery alone.

This trend of early decline in HRQL following neoadjuvant chemoradiation has been reported in other studies [20, 21]. Reynolds' group reported significantly reduced physical and role function following neoadjuvant therapy, but saw improvement in dysphagia scores in their cohort [21]. Blazeby's cohort of patients reported worsened dysphagia and reflux with chemoradiation therapy, as well as deterioration of social function 12 weeks into neoadjuvant therapy, without any significant emotional or cognitive change [20]. At 3 months after surgery, all studies reported no differences between groups undergoing neoadjuvant therapy plus surgery and surgery alone in HRQL. Thus, while chemoradiation therapy comes with its own set of adverse outcomes, there appears to be no adverse effect of neoadjuvant therapy on patient-reported post-operative quality of life.

Operative Approach on Health-Related Quality of Life

It is a common belief in the surgical community that operative technique and approach have a significant bearing on operative and postoperative morbidity and—by extension—on postoperative quality of life. Over the past decade, a considerable body of literature has been devoted to comparing open and minimally invasive surgical approaches primarily in terms of surgical and oncologic outcomes. Often, postoperative quality of life was not fully addressed in these studies, mostly because the dismal overall survival for esophageal cancer patients made such assessment meaningless. Fortunately, improved survival has now allowed us to address the impact of surgical approach on quality of life. A recent systematic review and meta-analysis by Kauppila et al. examined a pool of 2064 patients who underwent either a minimally invasive or open esophagectomy. The authors found that patients who underwent minimally invasive esophagectomy reported better quality of life scores in all domains at 4–6 weeks after surgery [22]. Further, the HRQL outcomes remained improved at 3 months in the domains of global quality of life, physical function, fatigue, and pain. These differences failed to persist at 6 and 12 months post-operatively. No clinically relevant differences were seen in esophageal cancer-specific outcomes, such as dysphagia, eating difficulties, reflux, and problems with coughing. Interestingly, none of the studies analyzed included a transhiatal approach. Overall, while minimally invasive surgery had generally better post-operative HRQL outcomes, the authors did not think their findings were sufficient to recommend minimally invasive esophagectomy as the standard of care [22].

Minimally invasive techniques, using a combination of laparoscopic and thoracoscopic approaches, have gained popularity in the surgical treatment of esophageal carcinoma, with an aim of reducing surgical trauma and improving post-operative recovery. In general, minimally invasive esophagectomy is well tolerated with short-term outcomes similar to open surgery [23]. In a European multi-center randomized control trial comparing minimally invasive to open esophagectomy, patients scored significantly better on several specific factors of quality of life following a minimally invasive approach [24]. At 1 year following surgery, patients who had undergone minimally invasive esophagectomy reported significantly higher HRQL scores on EORTC questionnaires in the domains of global health, physical activity, and pain than their counterparts who had undergone an open approach.

Postoperative Complications as a Predictor of Quality of Life

In a prospective Swedish nationwide study by Viklund et al., assessing quality of life following surgery, the occurrence of post-operative complications were found to significantly affect the mean global quality of life, physical functioning, and role functioning at 6 months after surgery [25]. Inpatient hospitalization greater than 21 days was also associated with decreased social function, role function, and physical function. In complement, a small Italian study also noted that complications led to a reported worsened emotional function [26].

Beyond 6 Months: Survivorship Issues After Esophagectomy

It is now possible to attain long-term survival after trimodality treatment for esophageal malignancy. Consequently, quality of life has now become an extremely important consideration for cancer survivors. A contemporary meta-analysis of robust design reported significant differences in role, social and physical functioning at an interval of 9–12 months following esophagectomy [9]. Unfortunately, data for outcomes longer than this duration are few and the specific impact of esophagectomy on GI function remains unclear. If smaller studies are considered, there

appears to be a prolonged reduction in HRQL with fatigue, diarrhea, nausea and vomiting and appetite loss remaining a significantly concern for at least 3 years following surgery [9].

Fitness and Physical Function

Physiologic resilience is a key aspect in the overall selection of suitable patients for esophagectomy. This is because our expectation is that patients with considerable functional reserve going into surgery will use this to augment post-operative recovery. In turn, this augmented recovery will contribute to a rapid and robust return to a quality life. Unfortunately, our expectations in this regard may be misguided. One study of a small cohort of 25 esophageal cancer survivors demonstrated significantly lower fitness on an incremental shuttle walk test, and less time spent in moderate and vigorous intensity physical activity, compared with age-matched controls. Global health status and quality of life were similar in both groups, but physical and role functioning domains were lower in the cancer survivors [27]. In another small rehabilitation trial, only half of the patients were meeting daily recommended physical activity guidelines at baseline while also remaining highly sedentary for 10 h of the day [28]. Physical fitness may be maintained by intensive perioperative physiotherapy and this appears to provide important dividends. Japanese patients who underwent 30 min of strenuous daily inpatient physiotherapy were able to walk 87% the distance of an age-matched community dweller 3 weeks post-operatively [29]. In addition, changes in the 6 min walk test correlated with post-operative decreases in physical function, as measured by self-rated HRQL surveys [29]. Thus, future studies into pre-habilitation or rehabilitation strategies are likely to significantly impact the diminished post-operative physical function of esophageal cancer patients.

Body Weight and Composition

It is not a surprise that esophageal cancer results in sustained weight loss in the period prior to diagnosis and during treatment [30]. Most patients lose the majority of this weight prior to the time of diagnosis. In a population-based survey of 340 Swedish patients, female sex (OR 2.14, 1.07–4.28) and neoadjuvant therapy (OR 2.41, 1.01–5.77) were associated with greater than 15% weight loss [31]. In cohort studies, tumor factors, disease recurrence, and survival were not associated with weight loss [30, 32].

Multiple studies indicate that less than 10% of the patients meet their protein or calorie requirements at the time of discharge from hospital [33]. Supplementary enteral nutrition via a jejunostomy feeding tube is increasingly and routinely employed but has not been proven to prevent weight loss following esophagectomy [34]. A feasibility study of 54 patients randomized to 6 weeks of home enteral nutrition versus in-hospital enteral feeding only demonstrated a 6-week mean weight loss of 3.9 kg greater than those who had home enteral feeding. Two patients who had a feeding jejunostomy placed after a total gastrectomy required laparotomy and small bowel resection for feed-related small bowel necrosis. They also showed a 33% (7 of 21 patients) cross over rate to home enteral nutrition use (one for management of an anastomotic leak, six for loss of greater than 5% body weight). Sixteen of fifty-four patients had feeding for more than the expected 6 weeks, mainly due to poor physical energy or oral intake of less than one third of their energy requirement. The consensus from participants was that the jejunostomy feeding was acceptable, and reduced some of the anxiety regarding nutrition in the post-operative period [35].

A further randomized controlled trial providing approximately 500 calories of daily supplementation for 6 weeks to patients after surgery revealed weight loss of more than 10% of their usual body weight in 30% of the cohort. The weight lost was preferentially body fat, and was greatest in those with the largest degree of baseline excess body fat. In fact, patients tended to regress to their ideal BMI over the first 6 months following surgery [32]. However, in those that had persistent weight loss (greater than 5% of BMI) in the 3–6 month post-operative period, there was a clinically relevant greater than 10 point decrease in HRQL in physical (76.7 versus

87.5, $p = 0.066$) and social function (76.4 versus 87.8, $p = 0.034$), but no differences in other measures of HRQL or global scales [32].

Deficiencies in energy intake persist in the few studies that have looked at longer-term follow-up after surgery. In a study of 96 patients 1 year post-esophagectomy, energy and protein intake remained below recommended levels in 24% and 7% of patients, respectively [36], while one-third of 10-year survivors were not satisfied with their daily quantity of food intake, resulting in no overall gain of body weight after discharge from the hospital [37].

These data suggest that a more extended nutritional supplementation and input from nutritional services is needed in these patients in order to better understand and meet their needs. Oddly, there are no substantial differences in HRQL amongst those who lose significant amounts of weight (more than 10 or 15% of usual body weight), nor in those who fall below their ideal weight. Remarkably, as the majority of patients with esophageal adenocarcinoma are overweight or obese, many happily accept a loss of 10–15% of BMI [32].

Overall, weight loss occurs in the majority of patients, even those receiving adequate energy and protein intake supplementation [33]. Further studies on the long-term implications of protein calorie malnutrition and their functional consequences are certainly warranted.

Gastrointestinal Function

A number of nutrition-related symptoms indicating a change in gastrointestinal function are described after esophagectomy, including early satiety (affecting 90% of patients), post-prandial dumping (75%), difficulty swallowing high-viscosity foods (72%), reflux, and absence of hunger (50%) [38]. In a study of 66 patients at least 18 months following esophagogastric resection, 73% presented symptoms of malabsorption [39]. Importantly, in this cohort, 44% had pancreatic enzyme insufficiency, and 38% had small intestinal bacterial overgrowth, both of which are amenable to intervention. In this study, nutrition-related symptoms were not correlated with body weight changes or quality of life. Therefore, specific enquiry into HQRL and GI symptoms are warranted during follow-up [39].

Emotional and Psychological Outcomes

Psychosocial problems, such as feelings of depression and fear, are common following esophagectomy. Interestingly, patients seek medical care more often for physical symptoms, and try to find support for emotional problems within their social networks [40].

A qualitative thematic analysis of experiences of 12 patients from a patient support group resulted in the emergence of three separate themes: coping with a death sentence, adjusting to and accepting an altered self, and the unique benefits of peer support. Physical changes during recovery were described as a "mirror image of the deterioration observed prior to surgery especially in relation to weight gain and eating ability". Due to the anatomical changes following surgery, patients had to relearn how much they were comfortably able to eat and that appetite was not a good cue. The consequences of altered eating patterns had an impact on interpersonal and social function, due to a lack of control over the body's reactions to eating [41]. This finding is replicated in other qualitative studies [42, 43].

In a previous study [41], caregivers were also interviewed, and described themselves as a buffer for patients. Caregivers often feel a burden of responsibility to ensure that patients are eating adequately, maintaining their weight, and taking medications. Their representations of food and eating were noted to be emotionally laden, and they perceived recovery as the ability to eat larger meals. Common symptoms, such as weight loss or dumping were perceived as signs of disease recurrence.

Conclusion

The prognosis for esophageal cancer patients treated with curative intent have significantly improved in the last decades. Therefore, post-operative quality of life became increasingly important. Many contemporary studies report that the majority of esophagectomy patients never regain baseline preoperative HRQL levels. Long-term quality of life outcomes should be discussed with patients and included in decision making process.

Appendix: Summary of Prospective Studies Assessing HRQL in Esophageal Cancer

Authors, year	n	Median length of follow-up (months)	Study design	Results
Scarpa [26] 2012	1282	12	Meta-analysis	– Global QOL markedly decreased following surgery ($p = 0.04$) – Global QOL increased through the first 6 postoperative months, but role and physical function never increased to baseline – On multivariate analysis, emotional function and dysphagia at diagnosis were directly associated to global QOL at diagnosis ($p = 0.001$ and $p < 0.0001$, respectively) – Patients experiencing any kind of postoperative complication had the same global QOL as those who did not, but had worse emotional function long term and worse physical function short term
Kauppila [22] 2017	2064	12	Meta-analysis	– Patients reported better global QOL, physical function, fatigue, and pain at 3 months following minimally-invasive versus open esophagectomy – This differences failed to be significant at 6 and 12 months follow-up
Van Heijl [51] 2009	199	3	Prospective RCT	– In the postoperative multivariate analysis, social functioning ($p = 0.035$), pain ($p = 0.026$), and activity level ($p = 0.037$) predicted survival, besides pathological T-stage ($p < 0.001$) and N-stage ($p < 0.001$)
De Boer [52] 2004	199	36	Prospective RCT	– Three months after the operation, patients in the transhiatal esophagectomy group (n = 96) reported fewer physical symptoms ($P = 0.01$) and better activity levels ($P < 0.01$) than patients in the transthoracic group (n = 103), but no differences were found at any other measurement point
Maas [24] 2015	115	12	Prospective RCT	– Overall HRQL was improved at 1 year for both minimally-invasive and open esophagectomy compared to preoperative and 6-week postoperative scores – Patients who underwent minimally-invasive esophagectomy had significantly improved physical activity ($p = 0.003$), global health ($p = 0.004$) and pain ($p = 0.001$) scores at 1-year follow-up compared to those who underwent open esophagectomy
Noordman [53] 2017	363	12	Prospective RCT	– HRQL declined during neoadjuvant chemoradiotherapy, but this effect was not apparent in postoperative HRQL compared to surgery-alone
Djarv [16] 2010	169	60	Prospective population based cohort	– Pre-treatment dyspnea was associated with shorter post-treatment survival – Better recovery of physical function, pain, and fatigue at 6 months post-treatment was associated with longer survival

Authors, year	n	Median length of follow-up (months)	Study design	Results
Viklund [25] 2005	100	6	Prospective population based cohort	– Surgically related complications were main predictors of decreased QOL at 6 months (score of 54 from reference of 65) ($p = 0.03$)
Djarv [14] 2009	355	6	Prospective population based cohort	– Pre-treatment comorbidities, tumor stage III to IV, and tumor location in the middle and upper 1/3 of the esophagus were associated with poorer post-treatment HRQL – Patients with adenocarcinoma had better 6-month post-treatment HRQL than those with squamous cell carcinoma
Derogar [54] 2012	141	60	Prospective population based cohort	– Dyspnea (MD, 15; 95% CI, 6–23), fatigue (MD, 13; 95% CI, 5–20), and eating restrictions (MD, 10; 95% CI, 2–17) were clinically and statistically significantly deteriorated throughout the follow-up in patients with major postoperative complications compared with patients without major complications
Blazeby [20] 2005	103	22 (Chemoradiotherapy and surgery) 11 (Chemotherapy and surgery) 27 (Esophagectomy alone)	Prospective cohort	– Neoadjuvant therapy has a temporary negative effect on HRQL, most commonly related to treatment toxicity – Neoadjuvant therapy does not impair recovery of HRQL postoperatively
Zieren [55] 1996	149	12	Prospective cohort	– The most significant factors in reducing postoperative QOL was recurrence ($p < 0.01$) and anastomotic stricture ($p < 0.05$) – QOL decreased initially postoperatively, but was restored at 6 months in disease-free patients
McKernan [17] 2008	152	81	Prospective cohort	– On multivariate analysis, tumor stage ($p < 0.001$), operative treatment ($p < 0.0001$) and appetite loss ($p < 0.0001$) were independent predictors of cancer-specific survival
Parameswaran [23] 2010	62	12	Prospective cohort	– Patients had lower HRQL in the first 6 weeks following minimally invasive esophagectomy – HRQL scores returned to baseline at 6 months postoperatively and were maintained at 24 months
Healy [18] 2008	185	20	Prospective cohort	– Global QOL was associated with in-hospital mortality ($p = 0.02$) but not with major morbidity, cancer recurrence, or 1-year survival – On multivariate analysis, pre-treatment dyspnea predicted in-hospital mortality ($p = 0.042$) and pre-treatment fatigue was associated with reduce 1-year survival ($p = 0.033$)

Authors, year	n	Median length of follow-up (months)	Study design	Results
Reynolds [21] 2006	202	12	Prospective cohort	– Neoadjuvant treatment reduced physical ($p = 0.004$) and role ($p = 0.007$) function prior to surgery while improving dyspnea ($p = 0.043$) – Esophagectomy negatively impacted HRQL scores at 3 months in both multimodal and surgery-alone groups, with improvement in scores at 6 months – At 12 months, global QOL was better in the multimodal group than in the surgery-alone group ($P = 0.044$)
Donohoe [56] 2011	132	70	Prospective cohort	– Global health status was significantly reduced at least 1 year after esophagectomy (mean ± SD score 48.4 ± 18.6) when compared to pre-treatment. The degree of subjective swallowing dysfunction was highly correlated with a poor QOL (Spearman's $\rho = 0.508$, $p < 0.01$).
Egberts [57] 2008	105	24	Prospective cohort	– There was no statistically significant difference in any of the HRQL scales between patients with a cervical or a thoracic anastomosis.
Fujita [58] 1995	128	NR	Prospective cohort	– Three field lymphadenectomy resulted in similar HRQL to two field surgery

NR not reported

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Palliative Treatment of Esophageal Cancer

20

Thomas Runge and Todd H. Baron

Introduction

Esophageal cancer, in contrast to many other types of cancer, is increasing in incidence and mortality [1]. Globally, an estimated 450,000 new cases and 400,000 deaths occurred in 2012. Over the past 40 years, the incidence of esophageal cancer in the U.S. has increased nearly 50%, largely attributed to a dramatic increase in the incidence of esophageal adenocarcinoma [2]. Among patients diagnosed with esophageal cancer, two-thirds or more have advanced unresectable disease at presentation [3]. This translates to a very poor prognosis, with an overall 5-year survival rate of 15–20% in the U.S. and 12% in Europe [4, 5]. In cases without distant metastasis, patients still may not be eligible for surgical resection due to medical comorbidities or their overall condition. Many of these patients live less than 6 months, and palliative measures are the primary goal of therapy. Relief of dysphagia is the most common palliative treatment goal. However, gastrointestinal bleeding, nutritional problems, and malignant fistulae can also require treatment.

T. Runge · T. H. Baron (✉)
Department of Medicine, Division of Gastroenterology and Hepatology, University of North Carolina, Chapel Hill, NC, USA
e-mail: Thomas.Runge@unchealth.unc.edu; todd_baron@med.unc.edu

Management of Malignant Dysphagia

Endoscopic Management

Malignant dysphagia is difficulty swallowing due to cancer, and typically results from a partially or completely obstructed esophageal lumen. There are numerous palliative treatments currently available for relief of inoperable malignant dysphagia. These include endoscopic stent placement, radiation therapy (external-beam or brachytherapy), chemotherapy, photodynamic therapy, and nutritional support.

During the past 20 years, self-expandable metal stents (SEMS) have become available for the treatment of malignant dysphagia and are now used universally compared to rigid plastic stents. SEMS have a number of advantages over older plastic designs [6]. They are supplied in a tightly bound delivery catheter, reducing the delivery system size to 5–10 mm on average. Rigid plastic stents were more difficult to place, more prone to migration, and could not achieve the same degree of luminal widening [7, 8]. After placement, expansile forces continue to enlarge the luminal diameter toward a predefined size. A diameter of 16–24 mm can be achieved with SEMS, which allows for greatly improved swallowing, especially when compared to older plastic stents [9].

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Technique

The length and diameter of the stent should be chosen carefully. All prior endoscopic and radiographic images should be reviewed to help plan whether dilation is needed, and to help predict the size of the stent needed. Imaging studies greatly assist in determining the appropriate length of a stent, to allow for both full coverage of the tumor while minimizing extension of the stent into the cervical esophagus or into the gastric body. The procedure can be performed under deep sedation or general anesthesia. Fluoroscopy is recommended to allow for precise localization of the tumor and help determine adequate stent sizing.

First, a standard upper endoscope is passed to visually inspect the stricture. If the stent delivery system is unlikely to cross the stricture, endoscopic dilation can be performed to facilitate stent delivery. Then a wire is inserted into the scope and passed across the stricture. The scope is then removed and the stent is passed over the wire and deployed under fluoroscopy while maintaining position (Fig. 20.1).

Stent deployment can also be monitored endoscopically in lieu of fluoroscopy by reinserting the endoscope and positioning it adjacent to the proximal end of the stent; from here, the location of the stent can be monitored and adjusted if necessary (Fig. 20.2). When planning stent placement across the GEJ, the proximal end should lie at least 2 cm above the tumor edge. No more than a short length of stent should be placed into the stomach to prevent stent impaction and ulceration of the stomach wall [10]. After stent placement, its position at the proximal end can be inspected. Traversing the stent to inspect the distal stent, especially if there is any resistance at the stent waist, should be avoided unless absolutely necessary due to the risk of stent migration. If desired, the stent's position can be adjusted after deployment, with distal-to-proximal adjustments technically much easier than proximal-to-distal adjustments.

There are a wide variety of SEMS on the market, and each has slightly different features and expansile properties. The first SEMS were uncovered stents; however tumor ingrowth through the stent was problematic and occurred in 20–30% of cases (Fig. 20.3). Newer SEMS are partially-covered (PC-SEMS) or fully-covered (FC-SEMS) to prevent tumor ingrowth; both stent types are effective not only for preventing ingrowth but also for minimizing need for reintervention [11]. Need for reintervention or repeat endoscopy may still be encountered with PC-SEMS, due to development of tissue hyperplasia or tumor invasion at the uncovered stent ends [12, 13]. FC-SEMS were developed for the purpose of avoiding tissue hyperplasia and luminal narrowing at the ends of the stent. However, fully-covered stents migrate more frequently than partially-covered stent across all indications, with migration rates ranging from 20% to 40% [12, 14]. Notably, a recent study suggests that in malignant disease,

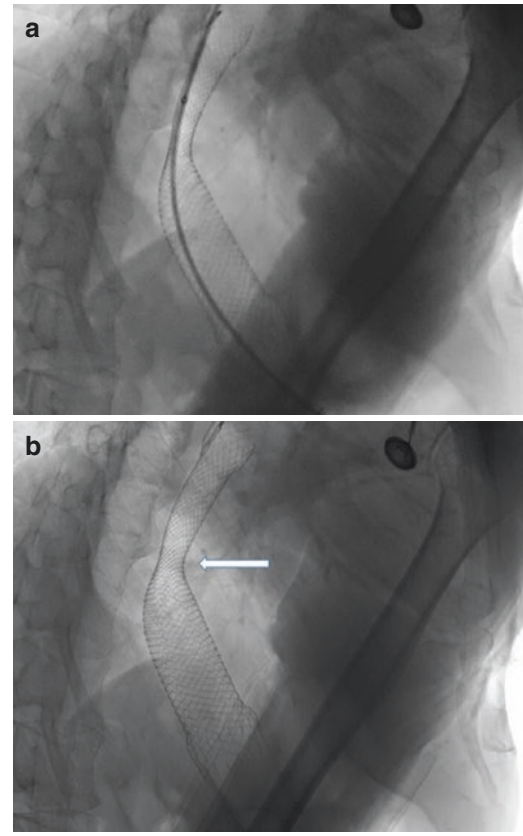

Fig. 20.1 (**a**) Fluoroscopic image during deployment of a fully-covered SEMS across a malignant esophageal stricture. (**b**) Image captured after complete deployment of the stent, showing a visible waist at the most severe narrowing (arrow)

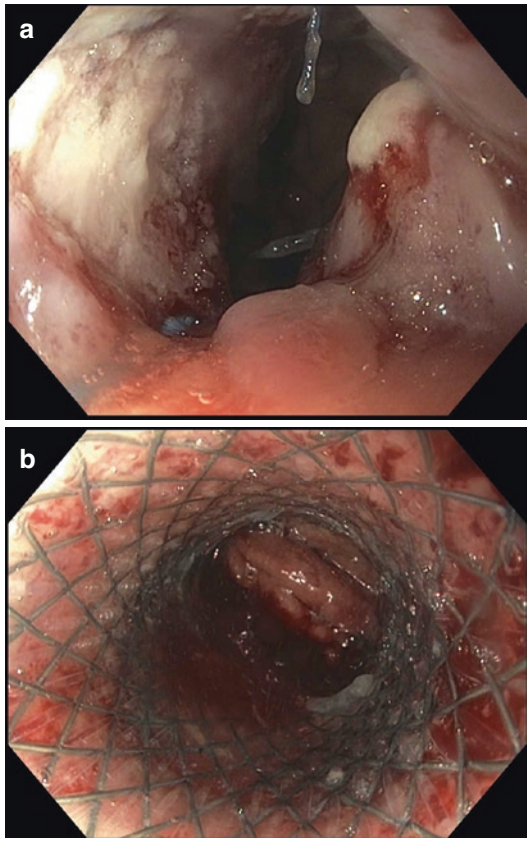

Fig. 20.2 (**a**) Malignant stenosis due to locally-advanced esophageal cancer. (**b**) Endoscopic image after placement of a fully-covered SEMS

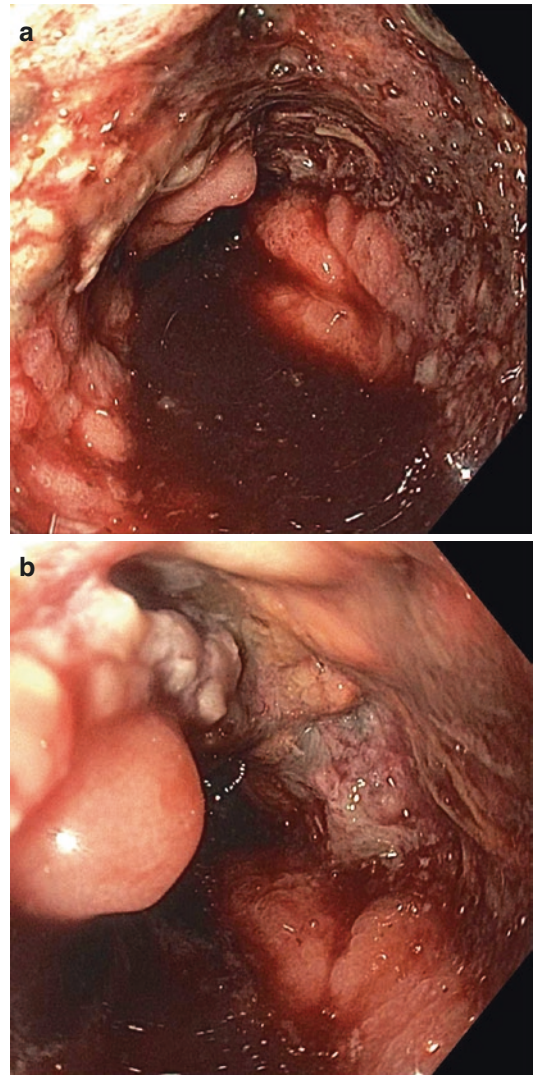

Fig. 20.3 (**a**) Tumor ingrowth identified along the distal aspect of a previously placed SEMS for esophageal cancer palliation. This patient presented with hematemesis after partially-covered metal stent placement. (**b**) Tumor expansion and tissue hyperplasia distal to a partially-covered SEMS

migration rates for FC-SEMS vs PC-SEMS are comparable [15]. Still, if a fully-covered or partially-covered stent is placed and the degree of stricturing is not severe, endoscopic suturing or clip fixation should be considered to reduce migration rates. With fully-covered SEMS, endoscopic suturing or clip fixation reduces migration rates by up to 75%; with partially-covered SEMS, suturing or clip fixation reduces migration by 55–60% [16].

Outcomes

The technical success rate for SEMS placement in the esophagus is close to 100%. Almost all patients experience dramatic improvements in swallowing, and most have improvements in the grade of dysphagia from grade 3 (able to eat liquids only) to grade 1 (able to eat most solid foods). Among different stent types, there have been multiple studies examining efficacy and complications for malignant dysphagia [17–19].

In a retrospective study design, uncovered Ultraflex stents, covered and uncovered Wallstents, and covered Z-stents were studied in 96 patients. No difference was found in success rates between stent types. Prospective randomized trials comparing stent types have also shown

high success rates as well as comparable rates of complications [18, 19]. While it is reassuring that multiple stent types are efficacious for cancer palliation, there are some tips that may assist the endoscopist in choosing a stent type. Individual meetings with manufacturers allow an endoscopist to familiarize themselves with a stent and delivery system, and can help the endoscopist decide which stent feels the most comfortable. For endoscopists with less personal experience using different expandable SEMS, deployment of one type of stent in several patients gives confidence to decide on the stent design. Colleagues, mentors and experts can be a resource to discuss use of different stent types across specific clinical scenarios.

Following SEMS placement, both minor and major complications requiring reintervention can occur [20]. Minor complications can be frequent (0–50%) and include chest pain, nausea, vomiting, or gastroesophageal reflux [21–23]. These symptoms can typically be managed conservatively with analgesics and antireflux measures. Chest pain can occasionally require stent removal or repositioning. Severe complications can occur and frequently do require reintervention; these can include hematemesis, stent migration requiring repositioning or restenting, food impaction, tissue hyperplasia or overgrowth, or new tracheoesophageal fistula (TEF) development. Perforation or death related to the procedure is exceedingly uncommon [24]. SEMS placed across the GE junction have higher complication rates when compared to stents placed in the mid-esophagus, specifically higher migration rates and reflux symptoms.

Chemotherapy, Intraluminal Radiotherapy and Drug-Embedded Stents

In addition to placement of SEMS, systemic or local chemotherapeutic options are increasingly being offered to patients with advanced cancer. Patients with incurable esophageal cancer, especially those with distant metastasis, who are otherwise in good general health may be offered these therapies. A disadvantage of stent placement and concomitant chemotherapy is the risk of stent migration if the tumor respond to chemotherapy. This occurs due to widening of the native esophageal lumen, and seems to occur more frequently in patients when stents were deployed across the GEJ [25]. In a recent meta-analysis, patients who underwent SEMS placement plus systemic chemotherapy had stent migration rates of 32% [25]. Unfortunately, despite the initial improvement in dysphagia following SEMS placement, dysphagia recurs in nearly 33% of patients and often requires repeat intervention [20]. To mitigate this effect, some groups have proposed alternative methods of palliation using single-dose brachytherapy. In a trial comparing SEMS to single-dose brachytherapy among 209 patients, dysphagia improved more rapidly after stent placement, but long-term dysphagia relief, and total days without significant dysphagia, favored brachytherapy compared to typical stents. Median survival was comparable between the groups.

Metal stents embedded with antitumor drugs are a promising new development, and in the coming years may be another option for local control of advanced esophageal cancer. One study in rabbits showed dramatic improvement in tumor size and volume when SEMS were covered with a paclitaxel-incorporated membrane [26]. A second study in a porcine model tested stents embedded with either 5-fluorouracil or paclitaxel, and very high local drug concentrations were achieved without any evidence of mucosal injury at necropsy [27].

Chemoradiation

An alternative treatment for malignant dysphagia is palliative chemoradiation, which has been shown to provide durable palliation of dysphagia in many patients with unresectable cancer [28, 29]. One study showed relief of dysphagia in 91% of patients with advanced cancer, and 67% of the patients had continue improvement in swallowing until their death without further intervention [28].

In addition to palliation of dysphagia, chemoradiation can be given with the intent of improving quality of life or extending life. Both chemotherapy and radiation therapy (RT) have been independently associated with improved quality of life in most studies. However, in a landmark trial, cisplatin-based chemotherapy added to RT conferred improved overall and 5-year survival [30]. Based on the strength of this trial data, concurrent chemoradiation is the standard offering for patients being treated with palliative intent. Potential complications in those receiving RT can include TEF formation or strictures. Endoscopic stenting prior to RT has been associated with higher rates of TEF development. Repeat endoscopic stenting can be utilized as a treatment for TEF. Strictures can be related to benign scar tissue formation, or to progression of underlying disease. These are typically treated with endoscopic balloon dilatation.

If initial chemoradiation fails, treatment intensification of both the RT and chemotherapy components can confer benefit. Recent trials have demonstrated improved quality of life and improved survival compared to supportive care if patients progressed on first-line agents [31, 32]. Biologic agents targeting endogenous receptors such as HER2, epidermal growth factor receptor (EGFR), and c-MET (mesenchymal-epithelial transition factor) are being studied because these factors are frequently overexpressed in esophageal and esophagogastric cancers. In phase 3 trials, improved responses to agents targeting HER2, for example, were seen in those with a compatible pattern of HER2 overexpression [33]. The precise role for these agents, however, has not yet been defined.

Management of Bleeding

Bleeding occurs in up to 10% of patients with advanced malignancy [34]. Treatments to palliate upper GI bleeding can include endoscopy, interventional radiological procedures, or multimodality therapies including radiation or vasoconstricting medications.

Endoscopic therapies are well-established in the treatment of non-neoplastic causes of bleeding (e.g., peptic ulcer, angioectasias, Mallory-weiss tears, etc.), with many series and controlled studies supporting their use. In this setting, a variety of modalities are available (injections, clips, thermal therapy, etc.), and in many cases bleeding can be managed solely with endoscopic therapies [35, 36]. Endoscopy for control of malignancy-related bleeding, in contrast, has shown to be less effective [37, 38] However, these therapies can avoid the need for an emergency surgery or temporize bleeding to facilitate chemotherapy or radiation in fit patients. Among all endoscopic therapies for tumor bleeding, argon plasma coagulation (APC) has the most evidence supporting its use [37]. A previous study analyzing bleeding foregut GI tumors found that treatment with APC was effective in more than two-thirds of patients, although complications including worsening bleeding and perforation occurred in 5–15% [39]. Other studies have shown application of APC can induce hemostasis in a majority of patients with tumor bleeding from esophageal cancers [40, 41]. However the preponderance of data indicates there is not reliable control of bleeding with these methods in tumor-related hemorrhage. For this reason, endoscopy is used in clinical practice predominantly for diagnostic purposes and to localize the bleeding source.

One encouraging innovation in this arena is the use of hemostatic powders. Hemospray (Cook Medical, Winston-Salem, NC, USA) is a powder that, when in contact with moisture, becomes sticky and adheres firmly to the application site [42]. This powder can be delivered easily via the endoscope and can be applied to a wide area rapidly, which is advantageous when the bleeding is diffuse. Two early series showed hemostasis in 100% of patients presenting with cancer-related upper GI bleeding, with a recurrence rate of 20% at 72 h after the initial endoscopy [41, 43]. This treatment modality is a promising temporizing measure for malignancy-related bleeding. Further research is needed to determine if such a technique can provide definitive control of bleeding in these patients.

Angiography can be used to localize and treat bleeding esophageal tumors, often as a second-line option following unsuccessful or unfeasible endoscopic treatment. With esophageal tumors, arterial bleeding can be life-threatening. Typically, angiography is performed by interventional radiologists once endoscopy has localized the tumor. Selective catheterization of a feeder vessel followed by transcatheter arterial embolization (TAE) can then be performed. This technique using coils or small particles to occlude vessels was first described for treatment of non-variceal bleeding uncontrollable by endoscopic methods, and has been effective in control of refractory esophageal bleeding with clinical success in 75–93% in several series [44, 45]. Angiography begins with selective catheterization of a larger arterial branch feeding the likely site of bleeding (Fig. 20.4). If a bleeding vessel is localized, superselective catheterization of this branch followed by embolization with microcoils is typically performed [37]. Recently, N-butyl cyanoacrylate (NBCA) has been shown to be effective for this purpose, with a theoretically higher success rate of occlusion even in patients with coagulopathy. Despite acceptable initial success rates of TAE, rebleeding is common and can occur in 20–60% of cases [37, 46].

Radiation therapy, delivered either as external beam radiation or intraluminal radiotherapy, could also potentially decrease malignancy-related bleeding related to direct effects on the tumor. Studies in bleeding related to gastric and rectal cancer suggest that clinical response can be achieved in two-thirds of patients [47, 48]. Data for control of bleeding in esophageal cancer are lacking, likely due to less frequent bleeding in these patients. However, with radiation delivered either externally or via intraluminal catheters, extrapolation of data from other GI tumors would suggest that shrinkage of the primary intraluminal tumor could resolve bleeding. Because

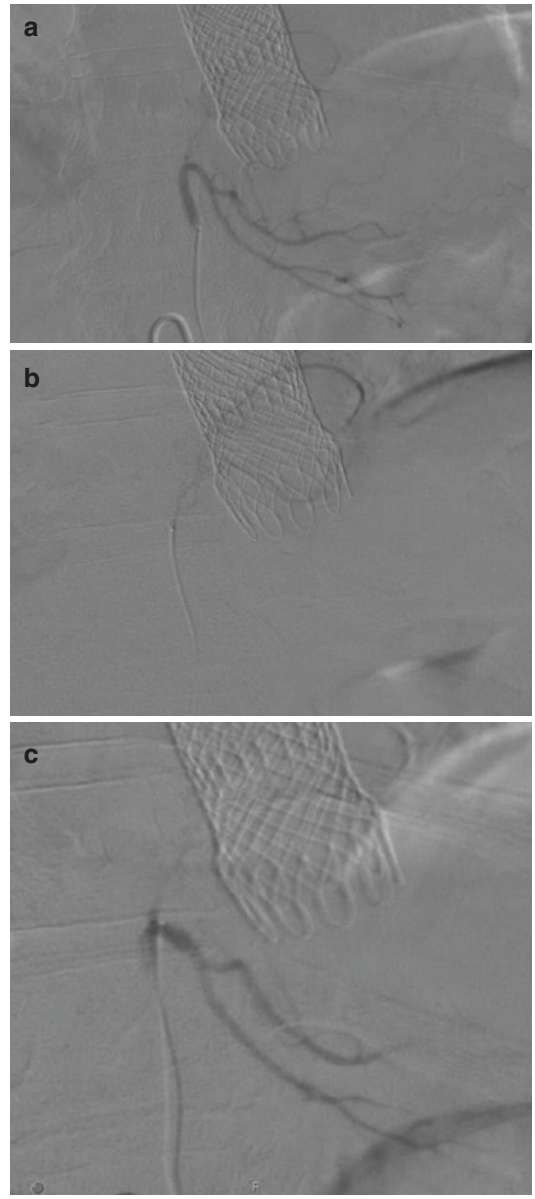

Fig. 20.4 (**a**) Digital subtraction angiogram of left gastric artery (LGA) with an abnormally enlarged esophageal branch feeding the distal esophagus. (**b**) Selective angiogram of dilated esophageal branch showing feeding vessels in more detail. Blush was seen at this location indicating hemorrhage. (**c**) Follow-up angiogram after embolization of dilated esophageal branch showing minimal residual flow

1–2 weeks of radiation therapy are needed to produce a clinical effect, radiation used for control of bleeding is suited only for chronic slow blood loss [37, 49].

Management of Malignant Fistula Formation

Esophageal carcinoma has the potential to spread into adjacent tissues and lead to development of a fistula, most commonly to the large airway creating a tracheoesophageal fistula (TEF), although bronchi are also possible sites of fistula formation. Esophagorespiratory fistulas in general are common complications of esophageal cancer, with incidence ranging from 5% to 20%. Occasionally fistulae can develop between the esophagus and mediastinal structures, the pleural lining, or the aorta [50]. In addition, fistulae may develop as a result of radiation therapy. Fistulae can occur secondarily after initial successful stent placement due to pressure necrosis caused by a flange of the stent. When a fistula is identified or suspected, management should be immediate, as fistula formation can potentially be life-threatening. A TEF, for instance, can lead to serious pulmonary infection due to contamination by gut secretions.

In malignant fistulae associated with esophageal cancer, curative resection is usually impossible or impractical due to the presence of an advanced tumor stage, or associated nutritional, metabolic, or infectious issues that pose significant risks. In these settings, if palliative surgery such as esophageal bypass or cervical esophagostomy is pursued, morbidity rates are quite high, and mortality rates can approach 50% [51, 52]. For these reasons, endoscopic placement of a SEMS is considered the procedure of choice for palliation.

Diagnosis and localization of a malignant fistula can be confirmed by radiography or computed tomography with water-soluble contrast [53]. Endoscopically, precise localization and interrogation of the fistula site is critical, and fluoroscopy is helpful for planning and to ensure appropriate stent sizing. Wire placement and judicious use of water-soluble contrast can confirm the exact site and tract of the fistula. A wire is then passed down the esophagus past the fistula site and any associated stenosis. A stent of appropriate length and width is then chosen; for this purpose stents can be fully-covered or partially-covered. The stent should be apposed to normal esophageal or gastric mucosa on both sides of the stent. Radiopaque markers such as paper clips can be used to assist in optimal positioning of the stent.

In clinical practice, esophageal stenting is typically undertaken first in cases of TEF due to its relative ease, high success rates, and patient tolerability. Multiple retrospective and prospective series have been published reporting the outcome of endoscopic stenting for this purpose, with high success rates and complete closure of the fistula in more than 90% of patients in most studies [21, 22, 54]. In these studies, complication rates vary between 10% and 30%. In addition to the technical or clinical success of SEMS placement for fistulae, esophageal stenting has also benefits on symptom control and quality of life in patients with TEF, due to improved intake, decreased need for nutritional support, and increased social function due to both fewer respiratory symptoms and less need for gastrostomy tube placement.

Tracheal stenting is also needed in certain scenarios. Some gastroenterologists request tracheal stenting prior to esophageal stenting, but due to increased complications with double stenting, this is not standard practice. Tracheal stenting may be needed when patients develop significant airway symptoms following esophageal SEMS placement, which can indicate airway or tracheal stenosis or leakage of luminal contents around the stent. In other cases, infiltrative esophageal

cancers invading the trachea may lead to recurrent dysphagia and respiratory symptoms. In these circumstances, the placement of a stent into the trachea and/or bronchi, either with or after esophageal stent placement, can be performed (this is termed parallel stent placement or double stenting). Stents placed in the trachea are typically uncovered, and these stents embed themselves into the respiratory tract mucosa [55]. Complications occur more commonly with parallel stent placement. Suboptimal deployment of the esophageal stent is possible. If the distal flange of a secondarily placed esophageal stent overlaps with a tracheal stent, this flange may deploy retrograde into the stent lumen, predisposing to stent occlusion. Another well-known complication is tissue necrosis; this can occur due to compression and ischemia of esophageal and tracheal wall layers between two SEMS. Tissue necrosis can increase the fistula size or predispose to fatal complications such as perforation and hemorrhage [56].

In cases of refractory fistulae, restenting with a single stent or placement of an overlapping stent can be pursued. In cases where this has failed or when a patient has repeated admissions or infectious complications, use of a second modality for the fistula closure could be considered. These modalities can include a fibrin plug, pigtail stent placement, over-the-scope clip (OTSC) placement, or endoscopic gluing. The goal in these settings would remain to avoid hospitalizations, especially in those with a short life expectancy.

Management of Malnutrition

Many patients with advanced esophageal cancer develop weight loss, often related to a decreased or modified oral intake, chemoradiation, or appetite loss due to their underlying disease [57, 58]. The conversion to an inflammatory, catabolic state also likely has a role in inducing weight loss in these patients. If unchecked, weight loss leads to decreased health-related quality of life, a reduced physical well-being, and poorer outcomes due to prolonged hospital stays and increased infectious complications [58–60]. Improved nutrition can provide better clinical outcomes following stenting or palliative systemic therapies.

Enteral nutrition is preferred because it can provide the necessary caloric needs of the patient, while maintaining the function of the gut lining. Relief of dysphagia symptoms with stenting and other palliative therapies is a critical step in maximizing enteral nutrition, but some studies suggest this alone may not be sufficient for inducing weight stabilization [61, 62]. In these cases, oral supplementation and dietary changes are needed.

Percutaneous endoscopic gastrostomy (PEG) tubes can also be used to supplement nutrition in patients with malnutrition, depending on the needs and wishes of the patient and family. PEG tubes have shown to be safe and effective in patients with advanced esophageal cancer [63]. An individualized approach is helpful in these scenarios, because this route bypasses the psychological and social benefits of oral nutrition. However, compared to nasogastric tubes, PEG tubes are more comfortable, more easily hidden from view, and safer for longer-term use if needed.

Conclusions

Currently available modalities for palliative treatment of esophageal cancer include placement of self-expanding stents or chemoradiation to provide relief of dysphagia, stents to treat malignant fistulas, multiple modalities for bleeding control, and nutritional support.

The use of fully-covered stents may decrease rates of tissue hyperplasia and overgrowth at the ends of the stent. The use of drug-embedded stents are showing promising results in animal models. When hemorrhage occurs in esophageal cancer, many current endoscopic modalities may temporize bleeding. However, interventional radiology should be consulted if these measures fail. Tracheoesophageal fistulas can cause life-threatening respiratory complications. Esophageal stenting alone can divert gut contents and often lead to fistula closure, but in some cases tracheal stenting may be needed.

Nutrition support for palliation can reduce hospital days and infectious complications while improving quality of life.

When treatment is palliative in intent, providing individualized care is paramount. In some cases, invasive procedures may present more potential harm than benefit, and discussions should focus more on comfort measures. Whether therapies have a clear record of success with few complications (e.g., esophageal stenting) or have an uncertain impact on clinical outcomes (e.g., endoscopy for bleeding control) should be explained to the patient, family members, and the care team. Finally, reasonable expectations should be set with the patient and care team. These challenging patients are best treated by a multidisciplinary team that includes medical oncologists, surgeons, gastroenterologists, and interventional radiologists.

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Future Directions in Esophageal Cancer

21

Ari Rosenberg and Victoria M. Villaflor

Introduction

Worldwide, there are 480,000 new cases of esophageal cancer annually [1]. In developed countries, the incidence of esophageal adenocarcinoma has surpassed squamous cell carcinoma (SCC) [2]. Despite the advances in earlier diagnosis and higher resectability rates, the prognosis of esophageal carcinoma remains poor with a 5-year survival rate of 15–34% [3–5]. Five year overall survival (OS) is correlated with the degree of pathologic tumor response at resection after neoadjuvant therapy. Patients achieving a pathologic complete response (CR) have a 5 year OS of 52%, while those with a pathologic partial response (PR) or no response have a 5 year OS of 38% and 19% respectively [5]. The degree of positive lymph nodes (LN) following resection predicts worse outcomes, with greater than four positive LNs or a greater than 20% LN positivity ratio predicting significantly decreased OS [6]. These data speak to the aggressive biology of esophageal cancer leading to high recurrence rates.

The shifts in epidemiology and earlier diagnosis of this devastating disease has provided an opportunity to improve outcomes of patients with resectable esophageal carcinoma. It is imperative that we improve our knowledge of the biology of esophageal cancer to improve both the cure rate and quality of life for these patients. In this chapter, we will review current treatment strategies and emerging treatment therapies against HER2 (trastuzumab or pertuzumab) or immune checkpoint inhibitors against programmed death 1 (PD-1; pembrolizumab and nivolumab) or programmed death ligand 1 (PD-L1; durvalumab). Understanding the foundations that have determined the current standard of care therapies for patients with locally advanced esophageal carcinoma will be helpful in interpreting results from these novel treatment clinical trials and ultimately the biology of this disease.

Current Treatment Strategies

Perioperative Chemotherapy

A meta-analysis comprising ten randomized controlled trials (RCTs) comparing perioperative chemotherapy plus esophagectomy to esophagectomy alone, suggested that perioperative chemotherapy combined with esophagectomy confers clinical benefit. This meta-analysis found in favor of perioperative chemotherapy with a hazard ratio (HR) of all-cause mortality of 0.87 (95% confidence interval (CI) 0.79–0.96) [4]. Most recently, a phase III clinical trial

A. Rosenberg · V. M. Villaflor (✉)
Division of Hematology/Oncology, Northwestern Feinberg School of Medicine, Chicago, IL, USA
e-mail: ari.rosenberg@northwestern.edu; victoria.villaflor@nm.org

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demonstrated superiority of perioperative chemotherapy plus esophagectomy compared to esophagectomy alone [7].

The Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) Trial, was a larger phase III RCT, which demonstrated a survival benefit of perioperative chemotherapy versus surgery alone [8]. In the MAGIC trial, 503 patients with gastric or esophageal adenocarcinoma were randomized to perioperative chemotherapy with esophagectomy or esophagectomy alone. In the group randomized to perioperative chemotherapy, epirubicin, cisplatin, and infusional 5-FU was given for 3 cycles prior and 3 cycles following esophagectomy. Primary tumor sites included the lower esophagus (15%), esophagogastric junction (11%), and stomach (74%). This trial demonstrated improved OS (HR for death of 0.75, 95% CI 0.060–0.930, p = 0.009) and 5-year OS benefit favoring patients treated with perioperative chemotherapy plus esophagectomy compared with esophagectomy alone (5-year OS of 36% vs 23%, respectively). Of note, only 42% of patients were able to complete the full protocol treatment which demonstrates the challenge of administering therapy in the post-operative setting.

The largest perioperative chemotherapy RCT was a trial conducted by the British Medical Research Council, the EC trial (OEO2). This trial randomized 802 patients to perioperative chemotherapy with esophagectomy vs. esophagectomy alone, and also favored patients treated with perioperative chemotherapy [9]. Another landmark RCT evaluating the role of perioperative chemotherapy was the North American Intergroup (INT) 0113 trial. This clinical trial was conducted between 1990 and 1995 and evaluated 467 patients with esophageal carcinoma including 51% with adenocarcinoma and 44% with SCC. In contrast to other RCTs, this trial had negative results. The HR for death was 1.07 (HR 0.87–1.32) and the 3-year OS rates were 23% in the group treated with perioperative chemotherapy plus esophagectomy and 26% in the group treated with esophagectomy alone [10]. These divergent results can be explained by heterogeneity of tumor location and histology (gastric, esophageal squamous cell carcinoma and adenocarcinoma). Additionally, staging technique accuracy has improved over the years. Interestingly, the earlier mentioned meta-analysis noted an improvement in the benefit of perioperative chemotherapy for patients with adenocarcinoma (3 RCTs [7, 10, 11] with 946 patients; HR 0.88, 95% CI 0.8–0.96) compared to patients with SCC (9 RCTs [10–17] with 1084 patients; HR 0.92, 95% CI 0.81–1.04) [4].

Overall, the existing RCT evidence demonstrates a benefit for perioperative chemotherapy plus esophagectomy compared to esophagectomy alone in patients with resectable esophageal carcinoma, with a marginally increased efficacy in adenocarcinoma compared to SCC.

Neoadjuvant Chemoradiotherapy

The benefit of neoadjuvant chemoradiation followed by esophagectomy compared to esophagectomy alone has been demonstrated for patients with resectable esophageal carcinoma in multiple studies and is considered standard of care in patients who are candidates for this approach [3, 18].

The largest RCT investigating neoadjuvant chemoradiotherapy for Oesophageal Cancer was Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) trial [3]. This RCT randomized 366 patients to neoadjuvant chemoradiation followed by esophagectomy versus esophagectomy alone. Patients who were randomized to chemoradation received weekly carboplatin and paclitaxel with concurrent radiotherapy followed by esophagectomy. The median OS with neoadjuvant chemoradiation plus esophagectomy was 49.4 months versus 24 months in the group treated with esophagectomy alone (HR for death 0.66, 95% CI 0.50–0.87, p = 0.003) [3]. This trial also enrolled multiple histologies (75% adenocarcinoma and 23% SCC), as well as multiple primary tumor sites included the esophagus (76%) and esophagogastric junction (24%).

There are other multiple smaller RCTs with conflicting results [4, 18–26]. These studies, however, were not adequately powered, often

enrolled multiple histologies and primary tumor sites, used variety of chemotherapy regimens, and altered radiation and chemotherapy schedules.

Overall, evidence suggests a benefit in favor of neoadjuvant chemoradiation plus esophagectomy as compared to esophagectomy alone in patients with resectable esophageal carcinoma. Most clinicians are currently favoring the CROSS regimen of carboplatin and paclitaxel with concurrent radiotherapy if the patient has satisfactory performance status for neoadjuvant treatment.

Perioperative Chemotherapy Versus Neoadjuvant Chemoradiotherapy

Currently, two RCTs have been completed directly comparing neoadjuvant chemoradiotherapy followed by esophagectomy to perioperative chemotherapy plus esophagectomy, and there was a non-significant trend toward superiority of neoadjuvant chemoradiation compared to perioperative chemotherapy [27, 28].

A small Australian phase II randomized controlled trial enrolled 75 patients who were treated with neoadjuvant chemoradiotherapy (cisplatin, 5-FU, and concurrent radiotherapy of 35 Gray starting in cycle two) followed by esophagectomy or perioperative chemotherapy (two cycles of cisplatin and 5-FU followed by esophagectomy) [27]. In this trial, there was a trend toward improved progression free survival (PFS) when patients were treated with chemoradiotherapy compared to chemotherapy, which was likely due to the higher rate of pathologic CR (13% with chemoradiation vs 0% with chemotherapy, $p = 0.02$). Remarkably, this trial included a lower dose of radiation delivered than typically applied in this setting (35 Gray compared to 41.4 Gray in the CROSS trial).

A larger European RCT is the preoperative chemotherapy or radiochemotherapy in esophagogastric adenocarcinoma trial (POET) showed a large but statistically insignificant trend in OS favoring chemoradiotherapy over perioperative chemotherapy (3-year OS 47.4% vs 27.7%, $p = 0.07$) [28]. In a recent update of the POET trial, at 5 years the median OS was 39.5% in the preoperative chemoradiotherapy group and 24.4% in the perioperative chemotherapy group ($p = 0.55$) [29]. Postoperative mortality was increased (but not statistically significant) in the neoadjuvant chemoradiotherapy group compared to the perioperative chemotherapy group (10.2% vs 3.8%, respectively, $p = 0.26$) [28, 29]. The increased postoperative mortality could be explained by low volume esophagectomy centers (12 of 19 centers) participating in these trials [30, 31].

These data demonstrate a trend toward improvement for patients who receive neoadjuvant chemoradiotherapy followed by esophagectomy as compared to perioperative chemotherapy plus esophagectomy. Nevertheless, in patients who have high perioperative risk due to comorbidities, or in low volume esophagectomy centers, caution should be advised with the use of trimodality therapy. There are additional studies currently in progress to better understand the differences in outcome comparing trimodality and bimodality therapy in patients with resectable esophageal carcinoma. One of these is an Irish trial in which patients will be randomized to the MAGIC perioperative chemotherapy regimen versus the CROSS neoadjuvant chemoradiotherapy regimen (NCT01726452). This trial is currently recruiting [32].

Adjuvant Chemoradiation

Adjuvant chemoradiation is typically applied to patients who are found to have locally advanced disease at surgery. An adjuvant chemoradiation strategy is supported by a RCT demonstrating improved OS [33]. The Intergroup Trial 0116 enrolled 556 patients with resectable gastric or gastroesophageal junction adenocarcinoma. Patients were randomized to surgery alone or adjuvant chemotherapy with 4 cycles 5-FU and leucovorin with a 5-week course of concurrent chemoradiation with 5-FU for cycle 2. This trial demonstrated that patients who underwent surgery followed by chemoradiation had an

improved OS compared to surgery alone (hazard ratio for death in the surgery alone arm of 1.35, 95% CI 1.09–1.66, p = 0.005) and improved 3-year OS with adjuvant chemoradiation (50% versus 41%, respectively) [33].

Future Directions of Perioperative Chemotherapy

Molecular

Prior investigation in the metastatic setting evaluating epidermal growth factor receptor (EGFR) inhibitors and MET inhibitors have been disappointing [34–37]. VEGFR (vascular endothelial growth factor receptor) has shown some promise in the metastatic setting [38]. Current investigation includes combinations incorporating human epidermal growth factor receptor (HER2) targeting, EGFR, and VEGFR in combination with perioperative chemotherapy.

The concept of incorporating HER2 directed therapy in the perioperative setting is based on the survival benefit of adding trastuzumab to chemotherapy in patients with metastatic esophageal adenocarcinoma with HER2 overexpression or amplification in the landmark ToGA (trastuzumab for gastric cancer) trial [39]. The INNOVATION-TRIAL (Integration of trastuzumab, with or without pertuzumab, into perioperative chemotherapy of HER-2 positive stomach cancer) is a RCT evaluating patients with resectable HER2 positive gastroesophageal or gastric adenocarcinoma with both preoperative and postoperative cisplatin and fluoropyridimidine in combination with HER2 blockade with trastuzumab or both trastuzumab and pertuzumab (NCT02205047). In a phase II/III RCT the British Medical Research Council is evaluating the efficacy of lapatinib (a dual tyrosine kinase inhibitor that targets both the HER2 and EGFR pathways) and bevacizumab (a monoclonal antibody that inhibits VEGFR) in combination with perioperative chemotherapy (epirubicin, cisplatin, and capecitabine) in patients with HER2 positive, resectable lower esophageal, esophagogastric junction, or gastric adenocarcinoma. This trial randomizes patients to perioperative chemotherapy alone, in combination with lapatinib, or in combination with bevacizumab (NCT00450203). The arm containing bevacizumab in this trial enrolled HER 2 negative patients and was closed following accrual in March 2014. Sadly, there was increased toxicity due to delayed healing with no overall survival benefit noted with the addition of bevacizumab [40].

Other potential molecular targets for esophageal cancer and gastroesophageal junction cancer include SRC-3 (steroid receptor coactivator-3), WNT, hedgehog inhibitors, FGFR (fibroblast growth factor receptor), MET, PIK3CA (phosphatidylinositol 4,5 bisphosphate 3-kinase catalytic subunit alpha) inhibitors, and many others currently in preclinical or metastatic clinical models.

Immune Therapy

Immune checkpoint inhibitors have demonstrated some success in multiple solid malignancies including melanoma [41], lung cancer [42], urothelial cancer [43], head and neck cancer [44], hepatocellular carcinoma [45], gastric cancer [46], and others. These successes have led to evaluation of these agents in the perioperative setting for esophageal and gastroesophageal malignancies. Recently, immune checkpoint inhibitors targeting the programmed death 1 (PD-1) and programmed death ligand-1 (PD-L1) interaction have been incorporated into neoadjuvant and adjuvant clinical trials for patients with locally advanced esophageal cancer (NCT02735239, NCT02730546, NCT02743494, and NCT03044613).

Future Directions of Neoadjuvant Chemoradiotherapy

Molecular

EGFR-targeted therapy has been added to neoadjuvant chemoradiotherapy in numerous trials and

has demonstrated increased toxicity without clinical benefit. Unfortunately, treatment-related toxicity has been the major barrier in combining EGFR inhibitors such as cetuximab, panitumumab, or gefitinib with neoadjuvant chemoradiotherapy in patients with locally advanced esophageal carcinoma (NCT00551759; NCT00827671). In the phase II American College of Surgeons Oncology Group (ACOSOG) Z4051 clinical trial, patients received docetaxel, cisplatin, and panitumumab every 2 weeks for 9 weeks with concurrent radiotherapy during weeks 5 through 9. This trial did not demonstrate an improvement in median OS (19 months) nor 3-year survival rate (38.6%) compared to historical controls. Furthermore, almost half (48.5%) of the patients experienced at least grade 4 toxicity [47]. Based on this data, adding EGFR-targeted therapy to neoadjuvant chemoradiotherapy is not recommended.

Given the success of targeting HER2 in the metastatic setting for esophagogastric cancers that overexpress HER2, incorporation of HER2 targeting in combination with neoadjuvant chemoradiotherapy is also being investigated. The RTOG 1010 is a phase III randomized clinical trial (NCT01196390) including patients with locally advanced, HER2 overexpressing esophageal adenocarcinoma are randomized to either neoadjuvant chemoradiotherapy with carboplatin and paclitaxel (CROSS Regimen) with trastuzumab and radiotherapy followed by esophagectomy and adjuvant trastuzumab for up to 13 cycles or neoadjuvant chemoradiotherapy with the CROSS regimen and esophagectomy alone (NCT01196390). Results from this trial and an analogous Dutch trial evaluating trastuzumab and pertuzumab in resectable esophageal adenocarcinoma (TRAP) trial (NCT02120911) are eagerly awaited.

Immune Therapy

In 2016, three clinical trials evaluating the incorporation of checkpoint inhibitor therapy targeting the PD-1/PD-L1 interaction with neoadjuvant chemoradiotherapy were launched. AstraZeneca has opened a German clinical trial adding durvalumab (anti-PD-L1) to neoadjuvant capecitabine, oxaliplatin, and radiotherapy in patients with locally advanced esophageal carcinoma (NCT02735239). Mayo Clinic has a clinical trial of pembrolizumab (anti-PD-1) in combination with either neoadjuvant chemoradiotherapy per the CROSS regimen, or in combination with perioperative FOLFOX (5-FU and oxaliplatin) without radiation in patients with locally advanced gastric or gastroesophageal junction adenocarcinoma (NCT02730546). The Mayo trial includes the potential for patients to continue pembrolizumab in the adjuvant setting following radiation. Bristol-Myers Squibb has a phase III RCT applying nivolumab in the adjuvant setting for patients with resectable esophageal or gastroesophageal junction carcinoma who do not achieve a pathologic CR after neoadjuvant chemoradiation and esophagectomy (CheckMate 577; NCT02743494). None of these checkpoint inhibitor clinical trials are screening patients based on PD-(L)1 expression, mostly because these immunochemistry markers are not absolutely predictive of response [48, 49].

Future Directions of Adjuvant Therapy

Adjuvant studies are not as popular as neoadjuvant chemoradiation in the perioperative setting for patients with locally advanced esophageal carcinoma. Adjuvant therapy can be difficult to deliver due to post-operative frailty, weight loss, and weakness following esophagectomy.

Current ongoing adjuvant trials include a trial with sunitinib, a broad tyrosine kinase inhibitor, following neoadjuvant chemoradiotherapy with cisplatin and irinotecan and esophagectomy (NCT00400114). There is also the CheckMate 577 trial with nivolumab or regorafenib following investigator's choice neoadjuvant chemoradiotherapy and esophagectomy (NCT02234180). The findings from these adjuvant targeted therapy and immunotherapy trials will have to be interpreted in the context of clinical trials being applied in the neoadjuvant and perioperative settings as well.

Conclusion

Currently, the standard of care for patients with locally advanced esophageal carcinoma is neoadjuvant chemoradiotherapy. Most often patients are treated with the CROSS regimen. It is still acceptable to treat patients who are moderate to high risk for surgical complications with perioperative chemotherapy alone, especially for adenocarcinoma histology.

In the near future, patients may benefit from targeted therapies such as HER2 directed therapy and immunotherapy. We still need to have a better understanding of the biology of esophageal cancer, the tumor immune microenvironment, and molecular alterations, in order to determine a tailored multimodality approach.

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